Asymmetric hydrogenation of imines, enamines and N-heterocycles using phosphoramidite ligands

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Chapter 2
Asymmetric hydrogenation of 2- and 2,6-substituted quinolines

In this chapter the asymmetric hydrogenation of 2- and 2,6-substituted quinolines catalyzed by iridium complexes of BINOL-derived phosphoramidites is described. Enantioselectivities of up to 89% were obtained using a mixed ligand system.

Part of this chapter has been published:

N. Mršić, L. Lefort, J. A. F. Boogers, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *Adv. Synth. Catal.* **2008**, *350*, 1081.

2.1 Introduction

Asymmetric hydrogenation of unsaturated prochiral compounds represents an attractive and versatile method for the preparation of enantiopure building blocks.[1] Although significant effort has been made in the area of asymmetric hydrogenation of aromatic and heteroaromatic compounds,[2] many challenges remain. Enantiopure tetrahydroquinolines represent important synthetic intermediates, as they are present in numerous alkaloids and biologically active compounds.[3,4] In the past, an ethanolic extract of *Galipea officinalis* was used against fever and inflammation. This extract contained four alkaloids depicted in Figure 2.1[5] and they all show activity against *Mycobacterium tuberculosis*.[6]

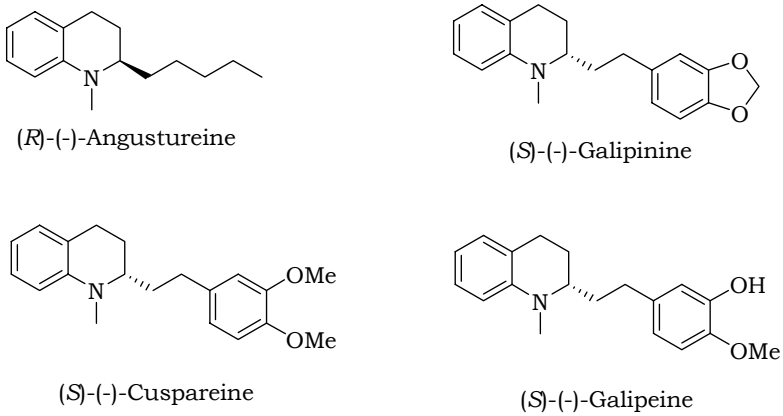
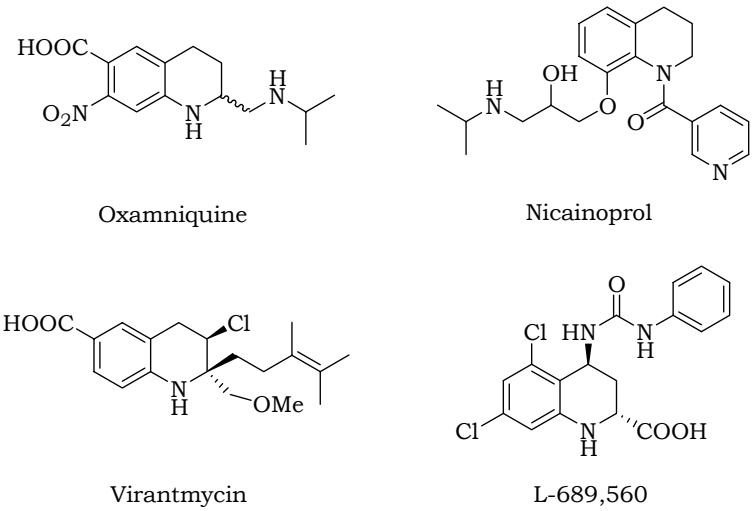


Figure 2.1 Alkaloids isolated from *Galipea officinalis*

2-Methyl-1,2,3,4-tetrahydroquinoline is present in the human brain as an endogenous alkaloid.[7] Discorhabdin C, a polycyclic system based on tetrahydroquinoline, is a marine alkaloid.[8] Dynemycin, a natural antitumor antibiotic, has a complex structure built on the tetrahydroquinoline scaffold.[9] Many relatively simple synthetic 1,2,3,4-tetrahydroquinolines are already used or have been tested as potential drugs (Figure 2.2). Among them, Oxamniquine, a schistosomicide (Schistosomiasis is a parasitic disease),[10] Nicainoprol, an antiarrhytmic drug,[11] and Virantmycin, a novel antibiotic,[12] are the best known. Tetrahydroquinoline L-689,560 is one of the most potent NMDAR (*N*-

methyl *d*-aspartate receptor) antagonists yet described.[13] Besides pharmaceutical applications, tetrahydroquinoline derivatives are useful as pesticides, antioxidants, and corrosion inhibitors.[4]



Oxamniquine | Nicainoprol

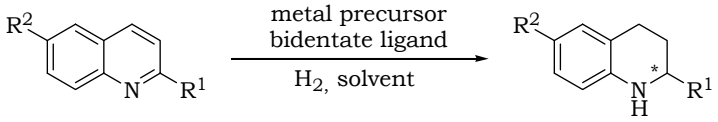
Virantmycin | L-689,560

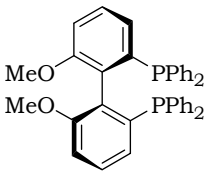
Figure 2.2 1,2,3,4-tetrahydroquinolines as potential drugs

Chiral enantiopure tetrahydroquinolines are usually prepared via asymmetric synthesis.[5,14] Transition metal-catalyzed asymmetric hydrogenation of quinolines is among the most effective methods for their preparation, as many substituted quinolines are commercially available.

In recent years, a number of bidentate chiral ligands were successfully used in the asymmetric hydrogenation of quinolines with high enantioselectivities (Scheme 2.1).[15-27]

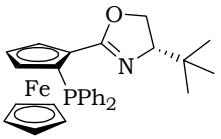
In 2003 Zhou *et al.* reported the use of Ir complexes generated *in situ* from $[Ir(COD)Cl]_2$ and (*R*)-MeO-Biphep[27] and in 2004 the application of ferrocenyloxazoline-derived N,P ligands[26] for the asymmetric hydrogenation of quinolines. Using iodine as additive in both cases, excellent *ee* was obtained. The approach using (*R*)-MeO-Biphep ligand was applied in the synthesis of Galipeine.[28] Same group described synthesis of (*S*)-MeO-Biphep-derived supported ligands and their use in the asymmetric hydrogenation of quinolines with up to 92% *ee*.[19] The catalyst is air-stable and recyclable.





(*R*)-MeO-Biphep

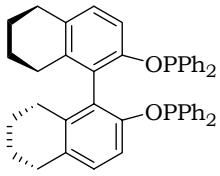
up to 96% *ee*



Ferrocenyl N,P-ligand

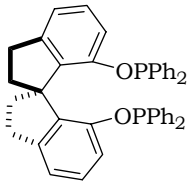
up to 92% *ee*

Zhou *et al.*, **2003**, **2004**



(*S*)-H_8-BINAPO

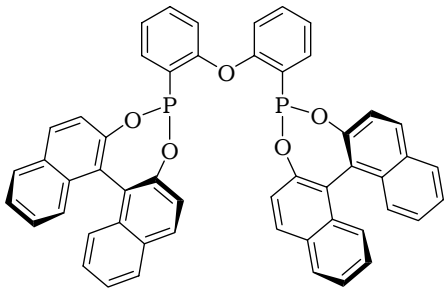
up to 97% *ee*

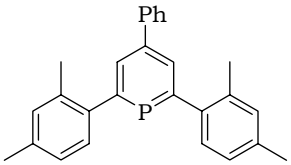


(*R*)-Spiropo

up to 94% *ee*

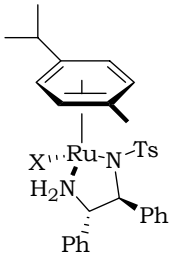
Chan *et al.*, **2005**, **2007**





up to 96% *ee*

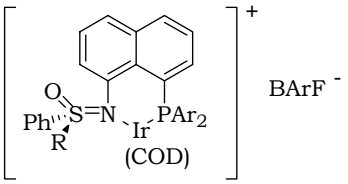
Reetz *et al.*, **2006**



X = OTf, Cl

up to 96% *ee*

Chan *et al.*, **2008**



Ar = C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3,5-$Me_2C_6H_3$, 4-$CF_3C_6H_4$

R = Me, Et, *i*-Bu, $Ph(CH_2)_2$

up to 92% *ee*

Bolm *et al.*, **2008**

Scheme 2.1 Efficient ligands/catalysts reported for the catalytic asymmetric hydrogenation of 2,6-substituted quinolines

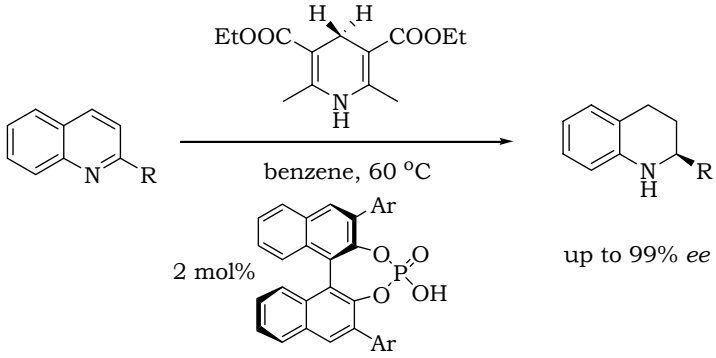
High enantioselectivities were also reported by Chan *et al.* using a catalyst based on the diphosphinite ligand H_8-BINAPO.[25] In addition, same group reported highly effective bisphosphinite ligand Spiropo in the Ir-catalyzed hydrogenation of quinolines with high substrate/catalyst ratio (5000).[20] Recently, the first phosphine free cationic Ru/Ts-dpen catalyst was described by same authors to lead to high reactivity and enantioselectivity in the hydrogenation of quinolines in neat ionic liquid.[18] The use of ionic liquid not only facilitated the recyclability, but also enhanced the stability and selectivity of the catalyst. The iridium equivalent of Ts-dpen catalyst was also shown to be efficient in the hydrogenation of quinolines.[16]

In 2006 Reetz reported the use of a combination of bis-phosphonites and monodentate achiral phosphorus ligands (up to 96% *ee*).[22] The group of Bolm described a series of naphthalene-bridged P,N-type sulfoximine ligands, which were applied in the Ir-catalyzed hydrogenation of quinolines with up to 92% *ee*.[17]

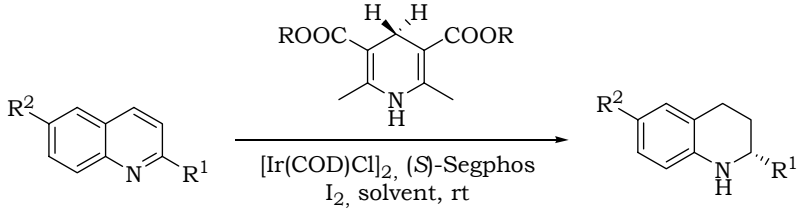
Dendritic catalysts derived from BINAP are also shown to lead to high enantioselectivities (up to 93%), and excellent catalytic activities (TOF up to 3450 h^{-1}) in the hydrogenation of quinoline derivatives.[21] In addition, the catalyst could be recovered by precipitation and filtration and reused at least six times with similar enantioselectivity.

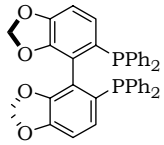
Transfer hydrogenation is a valuable and versatile reaction which is emerging as one of the best methods for achieving asymmetric transformations. The combination of practical simplicity, mild reaction conditions, relatively non-hazardous reagents and high selectivities distinghishes it from other processes in synthetic organic chemistry.[29-31] The first asymmetric organocatalytic transfer hydrogenation of heteroaromatic compounds was reported by Rueping in 2006 (Scheme 2.2).[31] The catalysts are bulky BINOL-derived phosphoric acids while Hantzsch esters were used as stoichiometric hydrogen source (up to 99% *ee*).

Rueping *et al.*, **2006**



Zhou *et al.*, **2007**





(*S*)-Segphos

up to 91% *ee*

for R^1 = Me, R^2 = H:

R	***ee* (%)**
Me	up to 91
Et	79
i-Pr	59
t-Bu	23

Scheme 2.2 Asymmetric transfer hydrogenation of quinolines

In 2007, Zhou *et al.* reported the use of (*S*)-Segphos as chiral ligand in the iridium catalyzed transfer hydrogenation of quinolines with Hantzsch esters (Scheme 2.2, up to 91% *ee*).[30] The *ee* is strongly determined by the nature of the ester groups of the Hantzsch ester.

2.2 Goal of the research

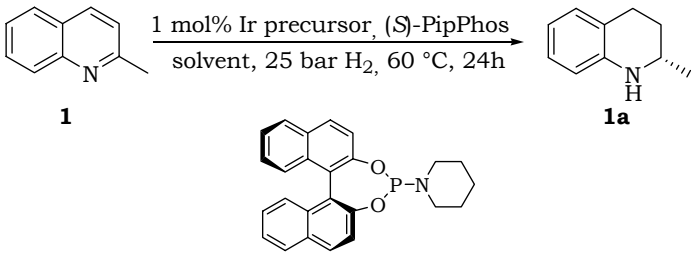
Asymmetric hydrogenation of quinolines is still not suitable for industrial applications due to the fact that the ligands employed are

usually prepared through a multi-step synthesis. Moreover, reported TOF's are often low and higher pressures are usually necessary due to the high stability of heteroaromatic substrates. Despite all the excellent examples in literature, the substrate scope is mainly focused on 2-alkyl, 2-aryl-substituted, and 3-substituted quinoline derivatives. Highly enantioselective hydrogenation of other quinoline substrates remains a challenging task. Therefore, the asymmetric hydrogenation of quinolines is still an underdeveloped area. From earlier results in our group, it was evident that monodentate phosphoramidites give excellent results in asymmetric hydrogenation,[32] conjugate addition,[33-38] [3+2] cycloaddition,[39] Heck reaction,[40] allylic alkylation,[34,41] asymmetric arylation of aldehydes,[42] ketones[43] and substituted imines.[44] In this chapter asymmetric hydrogenation of quinolines catalyzed by iridium complexes based on monodentate BINOL-derived phosphoramidites is described. Libraries of different phosphoramidites and phosphites as well as different metal precursors were tested. The effect of additives on the enantioselectivity of the reaction was examined. Some additional kinetic experiments were performed, as well as mass analysis and high pressure ^{31}P NMR studies of the catalyst, in order to obtain information on the metal complexes involved.

2.3 Initial screening and ligand optimization

Asymmetric hydrogenation of a benchmark substrate 2-methylquinoline **1** was chosen as a model reaction (Table 2.1). Initial hydrogenation experiments were performed at 25 bar of hydrogen pressure and 60 ^{o}C, using 1 mol% of iridium precursor (L*/Ir = 2/1). The catalyst was prepared *in situ*. Using (*S*)-PipPhos **L1a** as ligand and $[Ir(COD)Cl]_2$ as iridium source, 96% conversion and *ee* up to 36% was obtained in 24h (Table 2.1). Only 4% conversion and 17% *ee* was achieved at rt using 70 bar of hydrogen pressure. Initial solvent screening showed that the enantioselectivity of the reaction is solvent dependent.

Table 2.1 Solvent variation in the asymmetric hydrogenation of 2-methylquinoline **1**[a]



L1a, (*S*)-PipPhos

Entry	*Ir precursor*	*Solvent*	*Conversion*[b] *(%)*	*ee*[c] *(%)*
1	$[Ir(COD)Cl]_2$	HOAc	32	5
2	$[Ir(COD)Cl]_2$	*i*-PrOH	91	9
3	$[Ir(COD)Cl]_2$	MeOH	47	11
4	$[Ir(COD)Cl]_2$	THF	97	21
5	$[Ir(COD)Cl]_2$	acetone	97	18
6	$[Ir(COD)Cl]_2$	EtOAc	96	28
7	$[Ir(COD)Cl]_2$	CH_2Cl_2	96	18
8	$[Ir(COD)Cl]_2$	toluene	96	36
9[d]	$[Ir(COD)_2]BArF$	CH_2Cl_2	100	3

[a]Reaction conditions: 1 mmol quinoline **1**, 0.01 mmol $[Ir(COD)Cl_2]_2$, 0.04 mmol (*S*)-PipPhos **L1a**, 4 mL of solvent, 60 °C 25 bar H_2, 24h. [b]Conversion was determined by GC. [c]Enantiomeric excess was determined by GC analysis with Chiralsil DEX CB column. [d] 1 mmol quinoline **1**, 0.01 mmol $[Ir(COD)_2]BArF$, 0.02 mmol (*S*)-PipPhos. [e](*S*) configuration of the product was observed in all solvents. Absolute configuration of the product is assigned by measuring optical rotation and comparing it with literature data.

The best result was obtained in the non polar solvent toluene (Entry 8), whereas the use of protic solvents such as *i*-PrOH and MeOH resulted in low enantioselectivity and somewhat lower conversions (Entries 2, 3). Use of acetic acid as solvent leads to only 32% conversion and 5% *ee* (Entry 1). The use of cationic $[Ir(COD)_2]BArF$ resulted with full conversion but only 3% *ee* (Entry 9). In aprotic polar solvents like THF, acetone and ethyl acetate, excellent conversions and *ee*'s up to 28% were obtained (Entries 4-6).

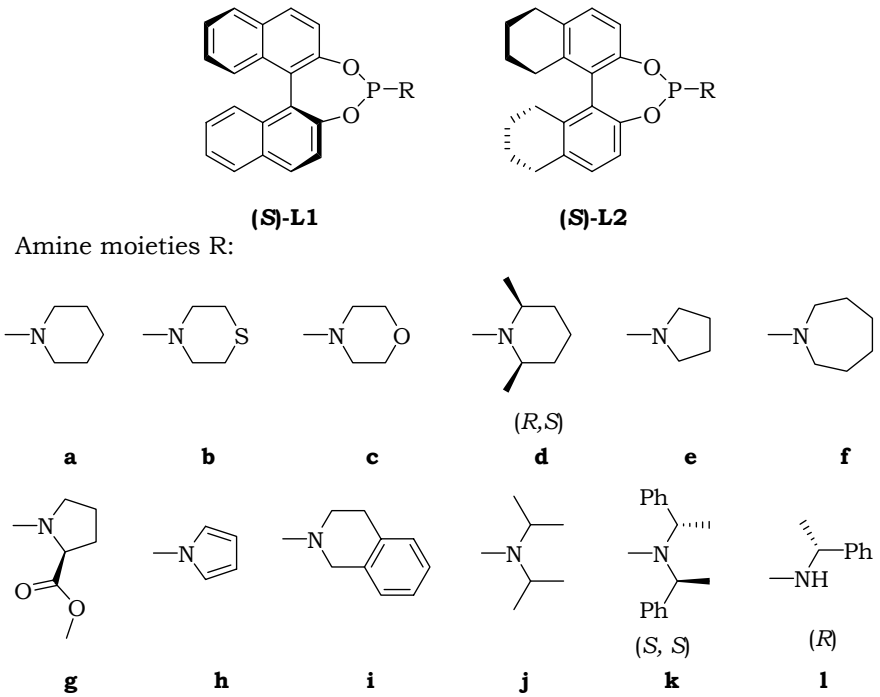
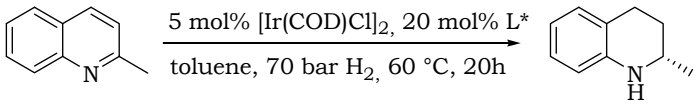


Figure 2.3 Monodentate phosphoramidite ligands screened in the asymmetric hydrogenation of 2-methylquinoline **1**

After screening of the solvents for the model reaction of the asymmetric hydrogenation of 2-methylquinoline **1**, different monodentate phosphoramidite ligands were tested (Figure 2.3). The screening was done using 5 mol% of iridium precursor and 20 mol% of ligand, at 70 bar of H_2 pressure and temperature of 60 °C. Results are presented in Table 2.2.

Simple monodentate BINOL-derived phosphoramidites, derived from cyclic amines (**L1a**, **L1c-i**, **L2a** and **L2f**) gave the best result (up to 70% *ee*, Entries 1, 2, 4-11). Ligands **L2a** and **L2f** that were derived form H_8-BINOL induced excellent conversion and 56% and 48% *ee*, respectively (Entries 2, 8).

Table 2.2 Screening of monodentate phosphoramidite ligands in the asymmetric hydrogenation of 2-methylquinoline **1**[a]

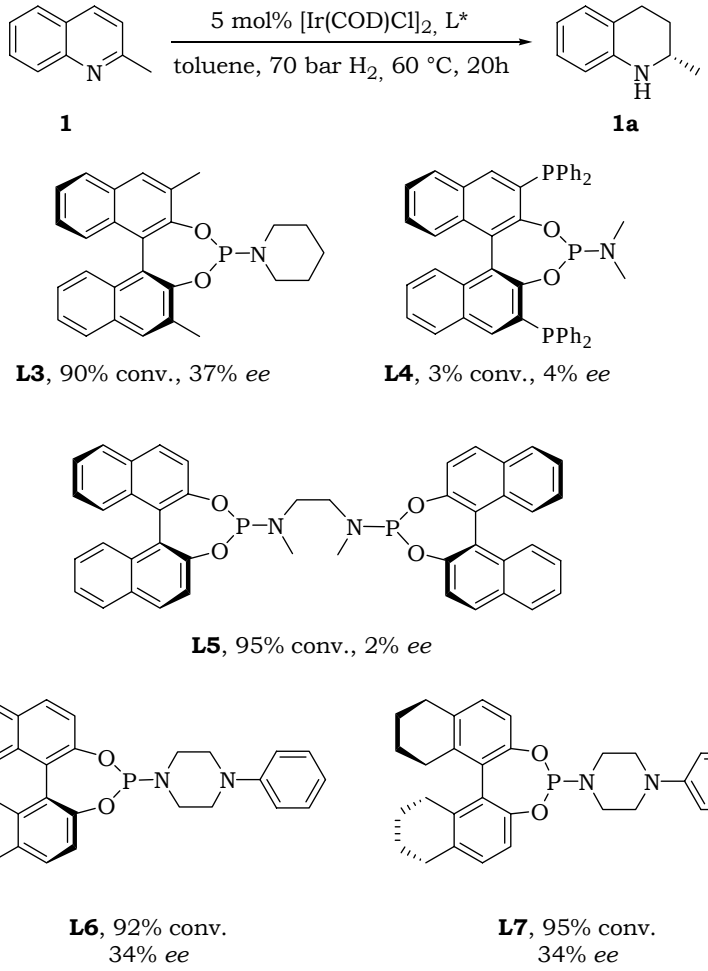


1 **1a**

Entry	*Ligand*	*Conversion*[b] *(%)*	*ee*[c] *(%)*
1	**L1a**	100	36
2	**L2a**	97	56
3	**L1b**	0	-
4	**L1c**	89	48
5	**L1d**	90	34
6	**L1e**	84	40
7	**L1f**	61	70
8	**L2f**	97	48
9	**L1g**	84	0
10	**L1h**	47	21
11	**L1i**	98	21
12	**L1j**	19	0
13	**L1k**	38	4
14	**L1l**	57	16

[a]Reaction conditions: 0.12 mmol quinoline **1**, 6 μmol $[Ir(COD)Cl_2]_2$, 24 μmol L*, 4 mL of toluene, 60 °C 70 bar H_2, 20h. [b]Conversion was determined by GC. [c]Enantiomeric excess was determined by GC analysis with Chiralsil DEX CB column.

Using the ligands derived from cyclic amines, lower enantioselectivities were obtained with those synthesized from pyrrole and tetrahydroisoquinoline (**L1h, L1i**, 21% *ee,* Entries 10, 11) The catalyst synthesized from phosphoramidite **L1b**, which is derived from thiomorpholine, led to no conversion (Entry 3). As sulfur compounds are known to be a catalyst poison, this could be the reason for the failure of the hydrogenation.[45] When ligands **L1g**, **L1k** were used, which were derived from chiral (*S*)-pyrrolidine-2-carboxylic acid methyl ester and (*S,S*)-bis-(1-phenyl-ethyl)-amine, the reaction was nonselective (Entries 9, 13). With ligand **L1l**, which was synthesized from the primary chiral (*R*)-1-Phenyl-ethylamine 57% conversion and 16% *ee* were obtained (Entry 14).



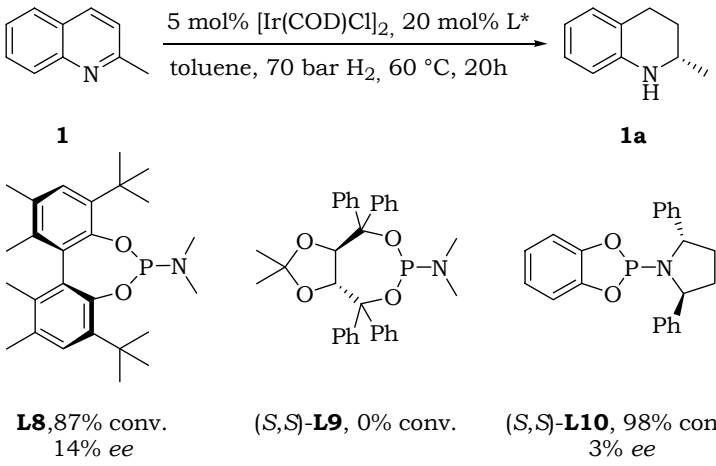
Scheme 2.3 Screening of phosphoramidite ligands in the asymmetric hydrogenation of 2-methylquinoline **1**

With substituted BINOL-derived phosphoramidites low *ee*'s were invariably obtained (Scheme 2.3). The highest *ee* was accomplished with the use of 3,3'-dimethyl-PipPhos (**L3**, 37% *ee*). Disappointingly, 3,3'-diphenylphosphine-substituted BINOL based ligand **L4** led to only 3% conversion. When bidentate phosphoramidite ligand **L5** was employed 95% conversion and only 2% *ee* was achieved.

We envisioned that ligands with an additional nitrogen atom in the structure would coordinate to the metal in a bidentate fashion and provide

the product with higher *ee*. Unfortunately with both ligands **L6** and **L7** *ee*'s up to 34% were obtained.

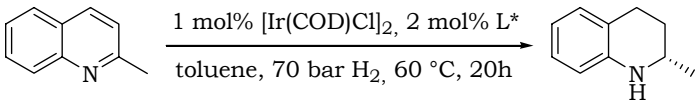
Phosphoramidite ligands synthesized from different diol backbones were also examined in the asymmetric hydrogenation of 2-methylquinoline **1**. Results obtained with bulky biphenol-, TADDOL- and catechol-derived phosphoramidites are depicted in Scheme 2.4. Using the biphenol-derived phosphoramidite **L8** 87% conversion and 14% *ee* was obtained. With the TADDOL-derived ligand **L9** no product was formed. In the case of the catechol-derived phosphoramidite **L10**, where the chirality comes from the (2*S*,5*S*)-2,5-diphenylpyrrolidine moiety, no enantioselectivity was observed in the hydrogenation reaction.



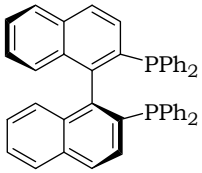
Scheme 2.4 Ligand screening in the asymmetric hydrogenation of 2-methylquinoline **1**

Several commercial bisphosphine ligands were also examined in the same model reaction, using 1 mol% of iridium precursor and 2 mol% of ligand at 60 °C and 70 bar of hydrogen pressure (Table 2.3). Good conversions, however modest enantioselectivity was obtained using bidentate BINAP and tolyl-BINAP ligands (43% and 39% *ee*, respectively (Entries 1, 2). The us of Me-DUPHOS led to 57% conversion and 39% *ee* (Entry 3), while with Josiphos ligand only 64% conversion and 13% *ee* was accomplished (Entry 4).

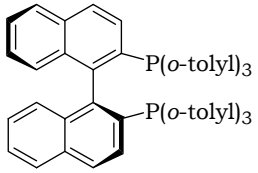
Table 2.3 Commercial bidentate ligands examined in the asymmetric hydrogenation of 2-methylquinoline **1**[a]



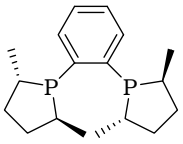
1 **1a**



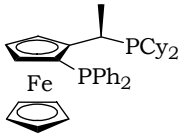
(*S*)-BINAP



(*S*)-tolyl-BINAP



(*S*,*S*)-Me-Duphos



(R_C,S_{Fe})-Josiphos

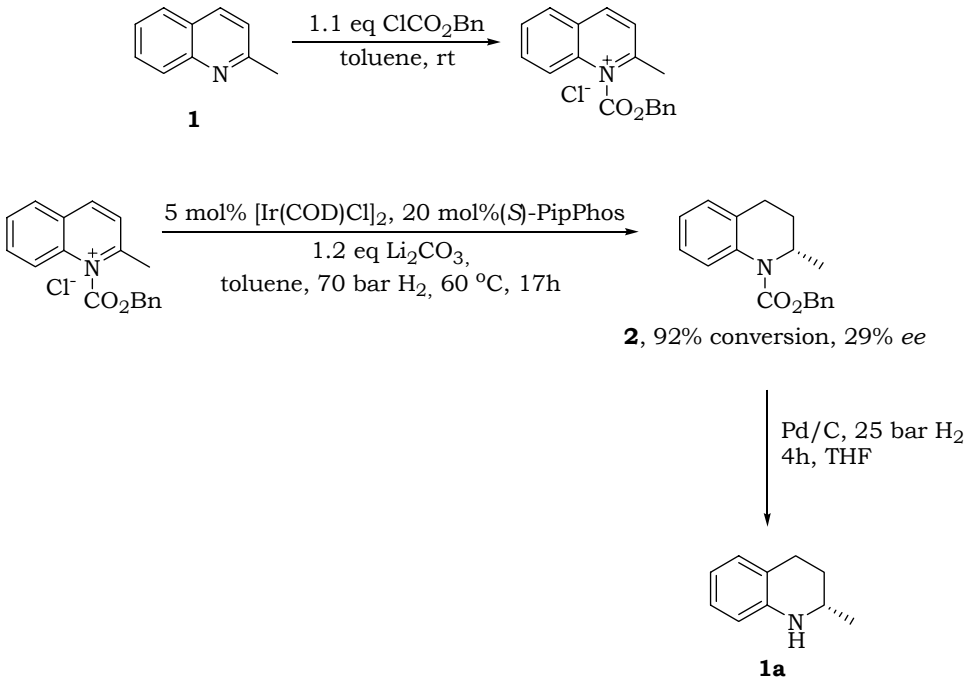
Entry	*Ligand*	*Conversion*[b] *(%)*	*ee*[c] *(%)*
1	(*S*)-BINAP	73	43
2	(*S*)-Tolyl-BINAP	67	39
3	(*S*,*S*)-Me-Duphos	57	39
4	(R_C,S_{Fe})-Josiphos	64	13

[a]Reaction conditions: 1 mmol quinoline **1**, 0.01 mmol $[Ir(COD)Cl_2]_2$, 0.02 mmol L*, 2 mL of toluene, 60 °C 70 bar H_2, 20h. [b]Conversion was determined by GC. [c]Enantiomeric excess was determined by GC analysis with Chiralsil DEX CB column.

From the results obtained so far it was evident that phosphoramidite ligands synthesized from the cyclic amines represent the best candidates for further optimisation of the asymmetric hydrogenation of 2-methylquinoline **1.**

In 2006 Zhou *et al.* reported the use of chloroformates as activating agents in the Ir/Segphos catalyzed asymmetric hydrogenation of quinolines and isoquinolines with up to 90% and 83% *ee*, respectively.[23] Without the use of the activating agent, the hydrogenation of isoquinolines

did not proceed, while by activating isoquinolines with chloroformates, the hydrogenation to dihydroisoquinolines proceeded with high yields and *ee*'s. This was rationalized as follows: 1) the aromaticity should be partially reduced by the formation of quinolinium salts; 2) bonding of the activating reagent to the N atom may prevent poisoning of the catalyst; and 3) Zhou *et al.* assumed that the attached CO_2R group is probably important for coordination between the substrate and the catalyst, and thus is beneficial to the control of enantioselectivity. 2-Methylquinoline **1** was therefore *in situ* derivatized with benzyl-chloroformate and subjected to the iridium catalyzed hydrogenation reaction using (*S*)-PipPhos **L1a** as a ligand (Scheme 2.5).



Scheme 2.5 Hydrogenation of activated quinoline substrate and subsequent deprotection

The iridium precursor and ligand were stirred under Schlenk conditions. In another Schlenk the substrate was stirred with benzylchloroformate in the presence of lithium carbonate. The solution of

the *in situ* prepared catalyst was then added to the derivatized substrate and the reaction mixture was placed in the autoclave. The mixture was hydrogenated with 5 mol% of iridium precursor and 20 mol% of PipPhos **L1a** at 60 °C and 70 bar of hydrogen pressure. Unfortunately following this approach only 29% *ee* was obtained.

2.4 High throughput experiments

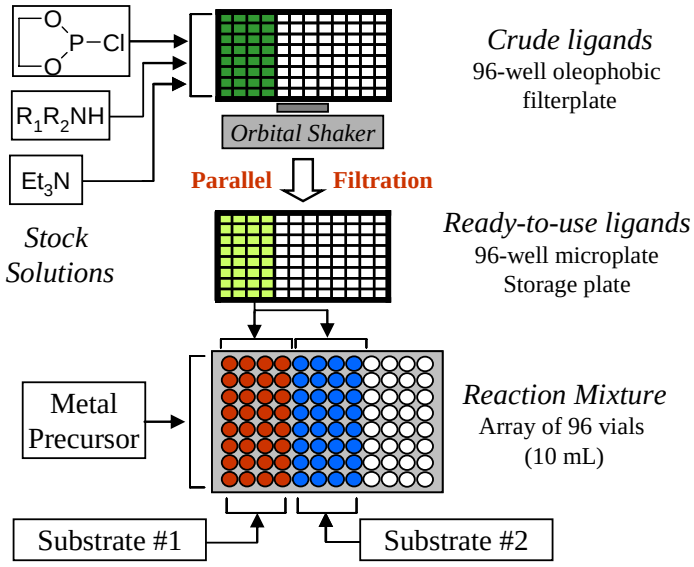
Based on these results, the screening of additional phosphoramidite ligands in toluene was performed. High Throughput Experimentation (HTE) is a methodology in which a large number of ligands are quickly synthesized and tested in parallel.[46] HTE is an efficient method for finding enantioselective transition-metal catalysts, especially in an industrial environment where time-to-market constraints are severe. Automation has been used in the synthesis of libraries of ligands on solid phase. However, the presence of the polymer can have an unfavourable effect on the rate and the selectivity when screening is performed on the bead.[47] Until recently, most ligand libraries have been synthesized one ligand at a time, especially those made by multistep synthesis which requires purification. Phosphoramidite ligands represent perfect candidates for parallel synthesis since they are easy to make, stable, cheap and highly modular. In the HTE experiment both the BINOL backbone and the amine part of the ligand can be varied, as well as the metal, solvents and reaction conditions.

In this chapter, a protocol for the automated solution-phase synthesis of a library of chiral phosphoramidites and phosphites and the screening of this library in the enantioselective hydrogenation of 2-methylquinoline **1** is described.

As mentioned earlier, phosphoramidites are easily obtained by reaction between a chlorophosphite and a primary or secondary amine in the presence of a base.[48] Chlorophosphites are prepared in a one step reaction by refluxing the diol in neat PCl_3. After removal of the excess PCl_3 the chlorophosphite is obtained in essentially pure form.

To obtain a pure phosphoramidite ligand, column chromatography and/or recrystallization were typically performed prior to its use in

catalysis. This tedious workup represented a serious obstacle toward a fully automated preparation of a large ligand library.



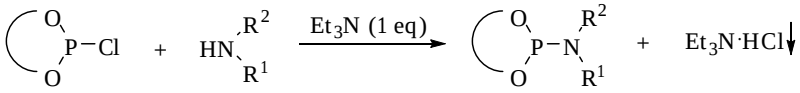


Figure 2.4 Protocol for the parallel synthesis of the ligand library[49]

It is assumed that as long as stoichiometric amounts of reagents are used and the reaction goes to completion, the main impurity present is the hydrochloride salt of the base (Figure 2.4). Thus, performing the reaction in a suitable solvent followed by simple filtration of the precipitated hydrochloride salt should lead to sufficiently clean phosphoramidite ligands. The simplified synthetic protocol could then be easily automated by using a 96-well oleophobic filter plate. Parallel filtration is performed upon application of vacuum, and the filtrates are collected in a second 96-well micro-plate that can be used for storage. This protocol was developed by Laurent Lefort at DSM.[49]

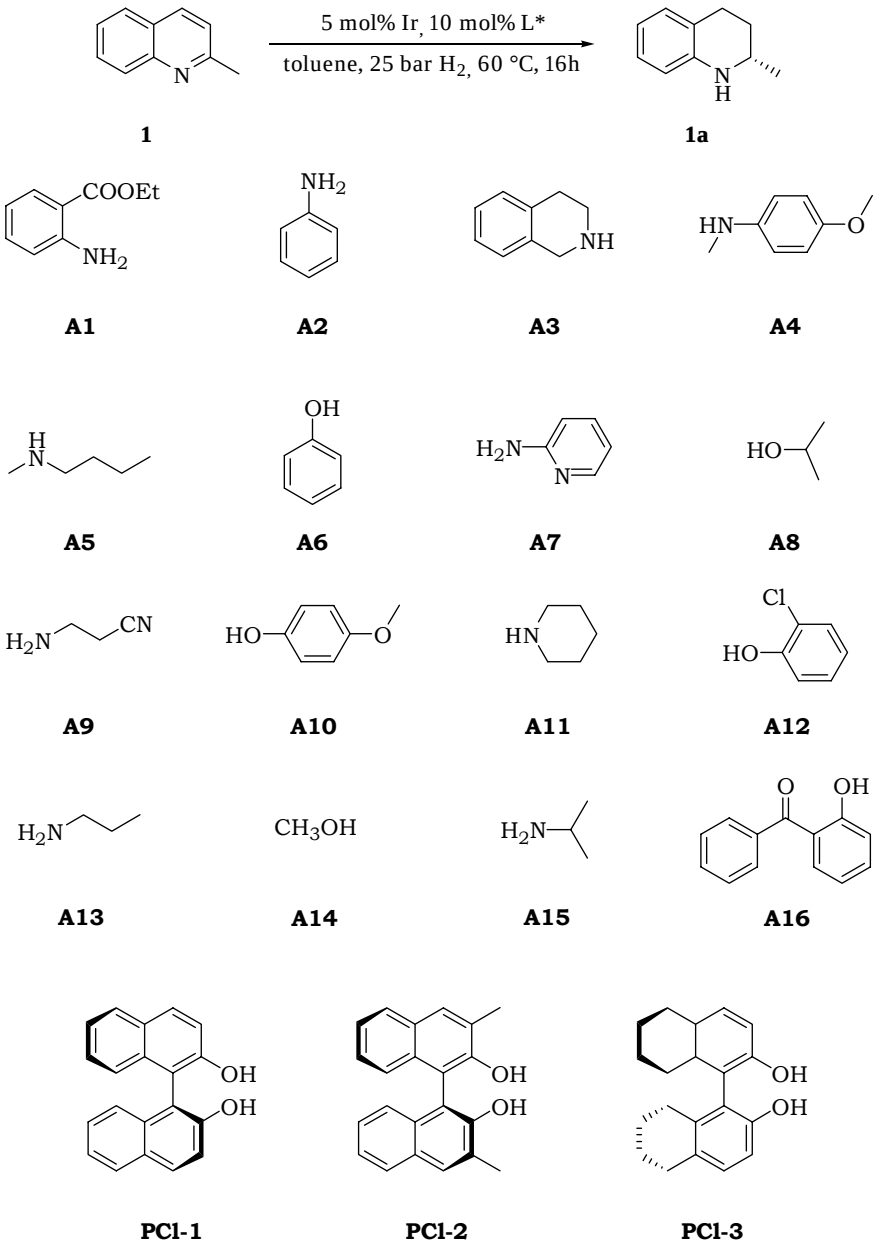
The ligand library (Scheme 2.6) was prepared by reacting (*S*)-2,2'-binaphthol-, (*S*)-H_8-2,2'-binaphthol- and (*S*)-3,3'-dimethyl-2,2'-binaphthol-

based chlorophosphite with 10 different amines (6 primary and 4 secondary) and 6 alcohols in the presence of triethylamine as a base, thus generating 48 ligands (30 phosphoramidites and 18 phosphites) with a wide diversity in their amino or alcohol moiety. Two different metal precursors were used, neutral $[Ir(COD)Cl]_2$ and cationic $[Ir(COD)_2]BF_4$. This initial set of amines and alcohols was randomly assembled to obtain diversity. Phosphoramidites derived from primary amines and BINOL have not been used extensively in catalysis in general as they partially decompose during chromatographic purification. The absence of the purification step in the automated procedure makes these primary amine based phosphoramidites readily available. Stock solutions of all the reagents were prepared in toluene and dispensed directly into the 96-well micro-plate with a liquid handling robot. The 48 reaction mixtures were vortexed using an orbital shaker for 2 h followed by parallel filtration giving 48 ligand solutions. A fraction of each solution was transferred to two sets of 48 vials, which contained iridium precursor (L*/Ir = 2/1) and the substrate 2-methylquinoline **1** in toluene (substrate/$[Ir(COD)Cl]_2$ = 40/1, substrate/$[Ir(COD)_2]BF_4$ = 20/1). The 96 hydrogenation reactions were performed in parallel in a Premex 96-Multi Reactor at 60 °C and 25 bar of H_2 for 16 h (Figure 2.5). The results are presented in Figure 2.6.

Figure 2.5 Premex 96-Multi Reactor

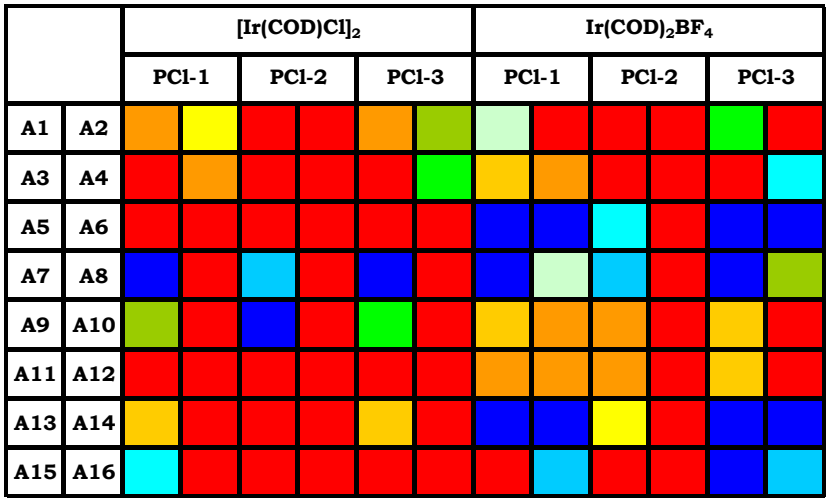
Although 48 different phosphoramidites and phosphites based on BINOL, H_8-BINOL, and 3,3'-dimethyl-BINOL were tested, as well as two iridium precursors, high enantioselectivities were not reached. In general, the highest *ee*'s were obtained using ligands derived from primary amines. Although conversions were not high, the best enantioselectivity was obtained using $[Ir(COD)Cl]_2$ and ligand synthesized from amines **A2** (aniline) and **A9** (3-amino-propionitrile) with BINOL-derived chlorophosphite **PCl-1** (up to 62% conv. and 51% and 52% *ee*, respectively). With the same iridium precursor and ligands synthesized from primary amines; 2-amino-benzoic acid ethyl ester **A1**, 1-propylamine **A13** and *i*-propylamine **A15** with chlorophosphite **PCl-1** *ee*'s up to 44% were achieved (conv. 85%, 79% and 24%, respectively).

Ligand obtained from **A2** (aniline) and H_8-BINOL (**PCl-3**) led to 42% *ee* and only 39% conversion. Enantioselectivities of 37% and 32% were accomplished with the ligand synthesized from **PCl-3** and amines (4-methoxy-phenyl)-methyl-amine **A4** and 3-amino-propionitrile **A9** (56% and 51% conv.) Very low enantioselectivities were obtained when ligands synthesized from 3,3'-dimethyl-BINOL were used, with both iridium precursors. When $[Ir(COD)_2]BF_4$ was used as a metal precursor, poor enantioselectivities were obtained in general, except when the ligand synthesized from 2-amino-benzoic acid ethyl ester **A1** and chlorophosphite **PCl-1** or **PCl-3** were used (45% conv., 45% *ee* and 58% conv., 36% *ee*).

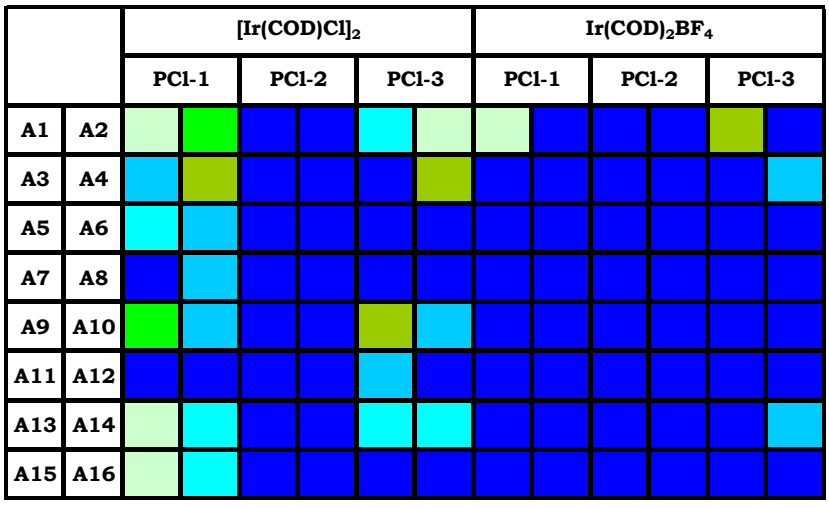


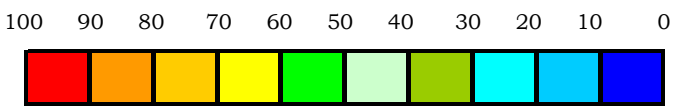
Scheme 2.6 Setup of library of ligands for the asymmetric hydrogenation of 2-methylquinoline **1**

Conversion (%)



Ee (%)





[a]Reaction conditions: 58 µmol quinoline **1**, 1.45 µmol $[Ir(COD)Cl_2]_2$, 5.8 µmol L*, 2.45 mL of toluene, 60 °C 25 bar H_2, 16h. [b]58 µmol quinoline **1**, 1.45 µmol $[Ir(COD)_2]BF_4$, 2.9 µmol L*, 2.45 mL of toluene, 60 °C 25 bar H_2, 16h. [c]Conversion was determined by GC. [d]Enantiomeric excess was determined by GC analysis with Chiralsil DEX CB column.

Figure 2.6 Results of the parallel screening of a ligand library in the asymmetric hydrogenation of 2-methylquinoline **1**

Surprisingly, it was observed that upon addition of 10 mol% of piperidine hydrochloride to the standard hydrogenation reaction based on *in situ* formed complex of (*S*)-PipPhos **L1a** and $[Ir(COD]Cl]_2$ in toluene, the enantioselectivity increased from 36% to 63%. This finding will be discussed in more detail further on in this chapter. In most hydrogenations described hereafter this additive was used.

2.5 Asymmetric hydrogenation of quinolines using mixed ligand approach

As mentioned in Chapter 1, both the group of Reetz[50] and our group[37,51] have shown that the use of mixtures of chiral monodentate ligands can improve enantioselectivity and reactivity. It is also possible to use mixed complexes based on a monodentate chiral ligand and a non-chiral phosphorus ligand.[35,36,52,53] In our group the mixed ligand approach has been employed in rhodium catalyzed asymmetric hydrogenations[51,52] and additions of boronic acids.[35,37]

Mixtures of (*S*)-PipPhos **L1a** and 17 different achiral phosphine ligands, 2 phosphites (**L27** and **L29**) and 1 phosphinine (**L28**) were therefore screened in the asymmetric hydrogenation of 2-methylquinoline **1** (Figures 2.7 and 2.8). Reactions were performed using 1 mol% of $[Ir(COD)Cl]_2$, 4 mol% of (*S*)-PipPhos **L1a** and 10 mol% of piperidine hydrochloride, under 50 bar of H_2 pressure over 24h. Results are presented in Table 2.4. It was observed that *ortho*-substituted phosphines **L12, L15, L16, L22, L23** as well as bulky tri-*tert*-butylphosphine **L17** and adamantyl-phosphine **L30** led to good to excellent conversions and high enantioselectivities (Table 2.4, Entries 3, 6, 7, 8, 13, 14, 21). The best result was obtained using PipPhos **L1a** and tri-*o*-tolylphosphine **L12**, giving full conversion and 83% *ee* (Entry 3). Surprisingly, the catalyst prepared from the mixture of PipPhos **L1a** and triphenylphosphine **L11** leads to very low conversion (Entry 2).

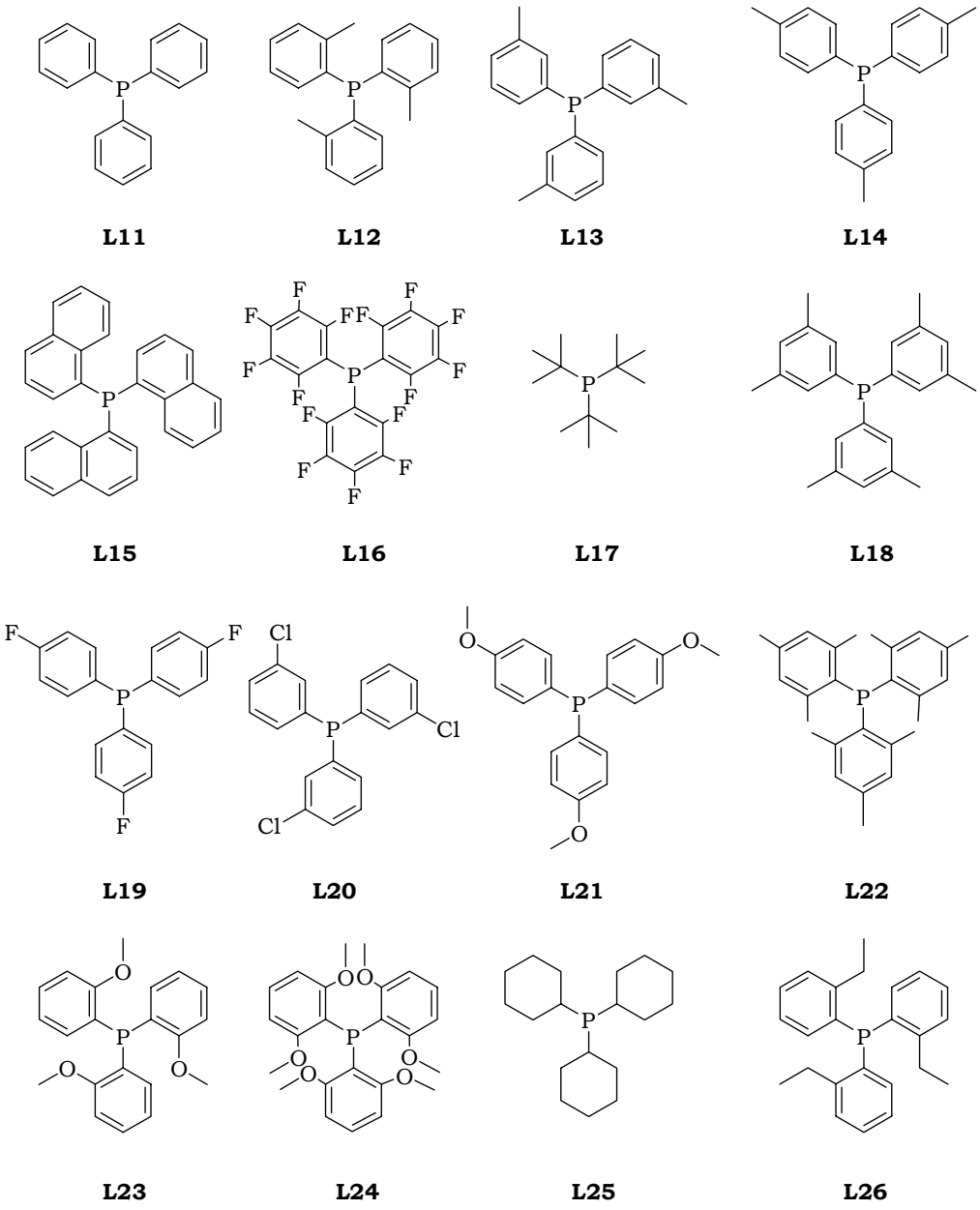
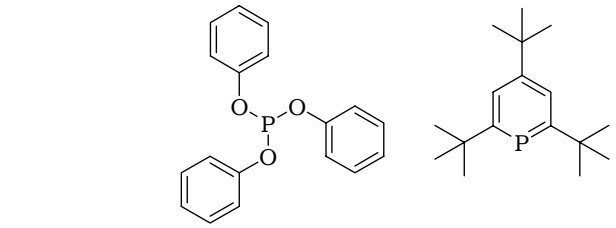
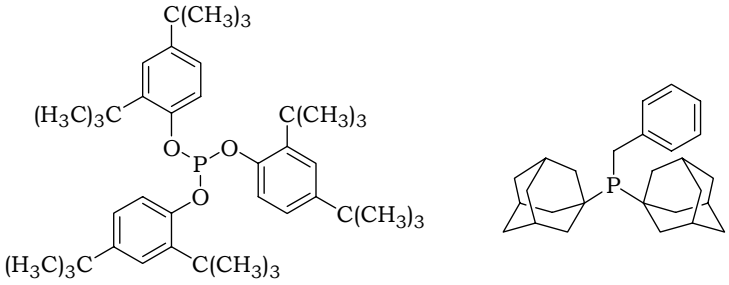


Figure 2.7 Achiral phosphines tested in the asymmetric hydrogenation of 2-methylquinoline **1**

Apart from phosphines, other type of P-ligands were tested in combination with PipPhos **L1a** (Figure 2.8). Non-bulky phosphite **L27** and bulky phosphite **L29** led to only 3% and 11% conversion, respectively (Entries 18, 20). With the use of phosphinine ligand **L28** excellent conversion and high *ee* was achieved (Entry 19).



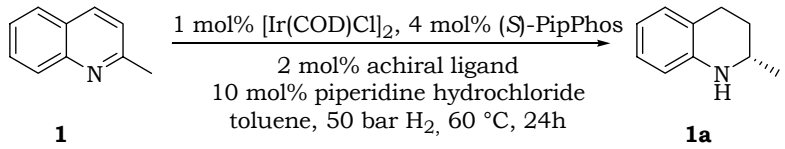
L27 **L28**



L29 **L30**

Figure 2.8 Achiral ligands tested in the asymmetric hydrogenation of 2-methylquinoline **1**

Table 2.4 Achiral P-ligands screened in the asymmetric hydrogenation of 2-methylquinoline **1**[a]



1 **1a**

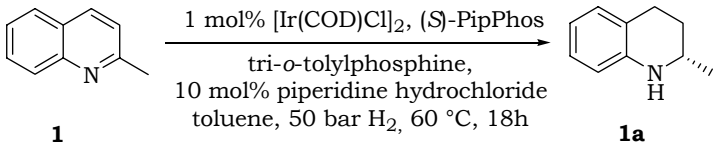
Entry	*Achiral phosphine*	*Conversion*[b] *(%)*	*ee*[c] *(%)*
1	-	100	63
2	**L11**	2	nd
3	**L12**	**100**	**83**
4	**L13**	2	0
5	**L14**	1	0
6	**L15**	41	81
7	**L16**	94	78
8	**L17**	54	82
9	**L18**	2	0
10	**L19**	1	0
11	**L20**	1	0
12	**L21**	2	0
13	**L22**	99	70
14	**L23**	18	77
15	**L24**	21	66
16	**L25**	9	5
17	**L26**	74	12
18	**L27**	3	62
19	**L28**	99	77
20	**L29**	11	77
21	**L30**	28	83

[a]Reaction conditions: 1 mmol quinoline **1**, 0.01 mmol $[Ir(COD)Cl_2]_2$, 0.04 mmol (*S*)-PipPhos **L1a**, 0.02 mmol achiral ligand, 0.1 mmol piperidine hydrochloride, 4 mL toluene, 24h. [b]Conversion is determined by GC. [c]Enantiomeric excess was determined by GC analysis with Chiralsil DEX CB column.

Since the best result was obtained with a mixture of (*S*)-PipPhos **L1a** and tri-*o*-tolylphosphine **L12** (full conversion and 83% *ee*), the ratio of those two ligands was optimized. Results are presented in Table 2.5. The amount of iridium precursor was kept constant, while changing the amount of PipPhos **L1a** and tri-*o*-tolylphosphine **L12**. The best results

were obtained in cases when the amount of PipPhos **L1a** was higher than the amount of tri-*o*-tolylphosphine **L12** (Entries 3-7). The highest *ee* was obtained with an Iridium/PipPhos/phosphine ratio of 1/2/1 (83%).

Table 2.5 Optimisation of the metal/ligands ratio in the asymmetric hydrogenation of 2-methylquinoline **1**[a]



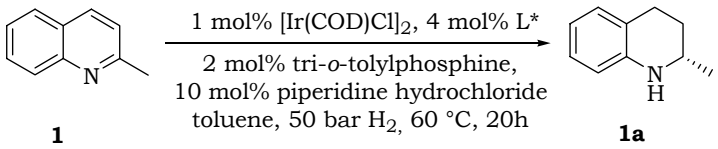
1 **1a**

Entry	*Ir/PipPhos/phosphine*	*Conversion[b] (%)*	*ee[c] (%)*
1	1/0.8/1	94	59
2	1/1/1	83	64
3	1/1.5/1	96	78
4	1/2/1	90	83
5	1/2/0.5	93	76
6	1/2/0.8	81	81
7	1/2/1.5	89	77

[a]Reaction conditions: 1 mmol quinoline **1**, 0.01 mmol $[Ir(COD)Cl_2]_2$, 4 mL of solvent, 60 °C 50 bar H_2, 18h. [b]Conversion was determined by GC. [c]Enantiomeric excess was determined by GC analysis with Chiralsil DEX CB column.

Different phosphoramidite ligands were tested in combination with tri-*o*-tolylphosphine **L12**, under the same conditions. Table 2.6 presents results for 4 different phosphoramidites with and without the presence of tri-*o*-tolylphosphine **L12**. In the case of the ligands **L1f** and **L8** the reaction was slowed down by the addition of achiral phosphine, while the *ee* stayed the same (Entry 1, 3). With H_8-PipPhos **L2a** the same result was obtained in the reaction with or without the addition of achiral phosphine (Entry 2). No conversion was obtained in the hydrogenation reaction using ligand **L9**, while with addition of achiral phosphine **L12** 9% of product was formed with almost no selectivity (Entry 4).

Table 2.6 Different phosphoramidite ligands tested in the combination with tri-*o*-tolylphosphine **L12**[a]



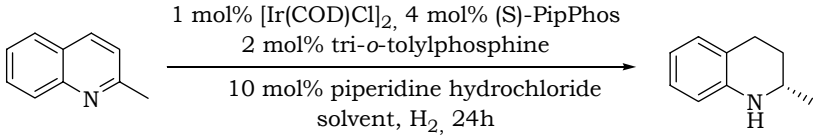
1 **1a**

Entry	*Ligands*	*Conversion*[b] *(%)*	*ee*[c] *(%)*
1	**L1f**	61	70
	L1f + L12	29	69
2	**L2a**	97	56
	L2a+ L12	97	57
3	**L8**	87	14
	L8+ L12	49	16
4	**L9**	0	-
	L9 + L12	9	4

[a]Reaction conditions: 1 mmol quinoline **1**, 0.01 mmol $[Ir(COD)Cl_2]_2$, 0.04 mmol phosphoramidite, 0.02 mmol achiral phosphine, 4 mL of toluene, 60 °C, 50 bar H_2, 20h. [b]Conversion was determined by GC. [c]Enantiomeric excess was determined by GC analysis with Chiralsil DEX CB column.

The effects of solvent, pressure and temperature on the conversion and enantioselectivity were also investigated using the $[Ir(COD]Cl]_2$/PipPhos/phosphine/piperidine hydrochloride catalytic system. 1 mol% of $[Ir(COD)Cl]_2$ was used with 4 mol% of (*S*)-PipPhos and 10 mol% of piperidine hydrochloride as additive. The results are summarized in Table 2.7. It was observed that the rate of the reaction strongly depends on the temperature. Conversions greater than 97% were achieved in all aprotic solvents at 60 °C and 25 bar H_2 pressure or higher, when 1% of iridium precursor was used. At lower temperatures the reaction is much slower (Entries 3, 6 and 14). The rate of the reaction depends on the hydrogen pressure, but importantly, the enantioselectivity stays the same for pressures above 10 bar, in keeping with earlier findings in olefin hydrogenation.[48] The dependence of the rate on the hydrogen pressure confirms that oxidative addition of hydrogen is the rate-determining step in the reaction mechanism.

Table 2.7 Asymmetric hydrogenation of 2-methylquinoline **1**[a]



1 **1a**

Entry	*Solvent*	*H_2 (bar)*	*T (°C)*	*Conv.*[b] *(%)*	*ee*[c] *(%)*
1	toluene	100	80	97	77
2	toluene	100	60	100	83
3	toluene	100	40	24	77
4	toluene	70	80	97	78
5	toluene	70	60	98	82
6	toluene	70	40	11	79
7	toluene	50	60	100	83
8	toluene	25	60	100	83
9[d]	toluene	25	60	30	84
10[e]	toluene	25	60	4	nd
11	CH_2Cl_2	50	60	100	**89**
12	CH_2Cl_2	25	60	100	87
13	CH_2Cl_2	10	60	40	87
14	CH_2Cl_2	50	40	7	nd
15	MeOAc	50	60	100	88
16	EtOAc	50	60	100	87
17	*i*-PrOAc	50	60	100	87
18	$ClCH_2CH_2Cl$	50	60	100	87
19	acetone	50	60	100	80
20	i-PrOH	50	60	91	65
21	HOAc	25	60	19	28

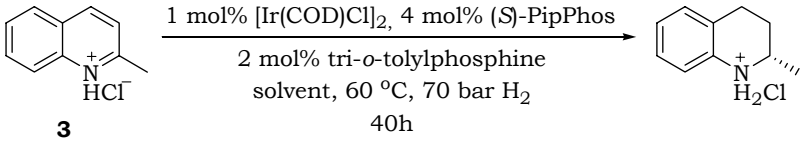
[a]Reaction conditions: 1 mmol quinoline **1**, 0.01 mmol $[Ir(COD)Cl_2]_2$, 0.04 mmol (*S*)-PipPhos **L1a**, 0.02 mmol tri-*o*-tolylphosphine, 0.1 mmol piperidine hydrochloride, 4 mL solvent, 24h. [b]Conversion was determined by GC. [c]Enantiomeric excess was determined by GC analysis with Chiralsil DEX CB column. [d] 1 mmol quinoline **1**, 0.005 mmol $[Ir(COD)Cl_2]_2$, 0.02 mmol (*S*)-PipPhos **L1a**, 0.01 mmol tri-*o*-tolylphosphine, 0.1 mmol piperidine hydrochloride.[e] 1 mmol quinoline **1**, 0.001 mmol $[Ir(COD)Cl_2]_2$, 0.004 mmol (*S*)-PipPhos, 0.002 mmol tri-*o*-tolylphosphine, 0.1 mmol piperidine hydrochloride.

The best result (quantitative conversion and 89% *ee*) was achieved in dichloromethane at 50 bar of pressure and 60 °C. When only 0.5% of metal precursor was used, the reaction slowed down, however the *ee* stayed high (84%, Entry 9). Further decrease of the catalyst loading led to no

conversion (Entry 10). In the protic solvent *i*-PrOH 91% conversion and 65% *ee* was obtained (Entry 20), while the use of acetic acid as a solvent resulted with low conversion and 28% *ee* (Entry 21).

It was even possible to hydrogenate the hydrochloride salt of 2-methylquinoline **1** in toluene without loss in enantioselectivity, however a longer reaction time (87% in 24h) was necessary, perhaps due to the poor solubility of the substrate (Table 2.8).

Table 2.8 Asymmetric hydrogenation of 2-Me-quinoline-hydrochloride **3**[a]



3

Entry	*Solvent*	*Conversion*[b] *(%)*	*ee*[c] *(%)*
1	CH_2Cl_2	100	71
2	EtOAc	99	83
3	toluene	100	82

[a]Reaction conditions: 1 mmol quinoline hydrochloride **3**, 0.01 mmol $[Ir(COD)Cl_2]_2$, 0.04 mmol (*S*)-PipPhos **L1a**, 0.02 mmol tri-*o*-tolylphosphine, 4 mL solvent, 40h. [b]Conversion was determined by GC. [c] Enantiomeric excess was determined by GC analysis with Chiralsil DEX CB column.

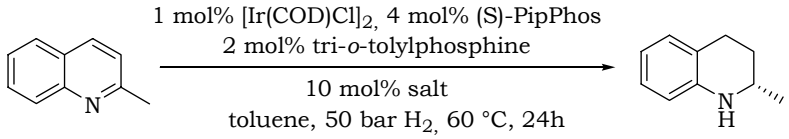
Hydrogenation was performed at 70 bar of hydrogen pressure in three different solvents. The best result was obtained in ethyl-acetate, giving 99% conversion and 83% *ee* (Entry 2). The reaction proceeds with similar selectivity as when 2-methylquinoline **1** was hydrogenated in the presence of piperidine hydrochloride.

2.6 Additives in the asymmetric hydrogenation of 2-methylquinoline

2.6.1 Salts as additives

Since the $[Ir(COD]Cl]_2$/tri-*o*-tolylphosphine/PipPhos/piperidine hydrochloride catalytic system gave the best result in the asymmetric hydrogenation of 2-methylquinoline **1**, further studies on the effect of addition of different salts with this system were performed (Table 2.9).

Table 2.9 Effect of the addition of salts on the enantioselectivity of the asymmetric hydrogenation of 2-methylquinoline **1**[a]



1 **1a**

Entry	*Salt*	*Conversion*[b] *(%)*	*ee*[c] *(%)*
1	-	100	63
2	Piperidine·HCl	100	83
3	KCl	100	83
4	Et_3N·HCl	98	81
5	CsF	0	-
6	KBr	100	69
7	KI	98	30
8	KBF_4	98	77
9[d]	$(CH_3)_4NI$	97	74

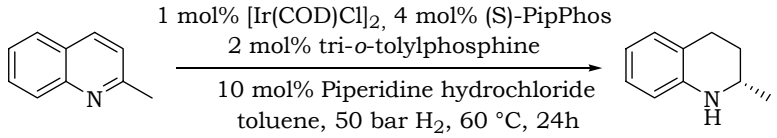
[a]Reaction conditions: 1 mmol quinoline **1**, 0.01 mmol $[Ir(COD)Cl_2]_2$, 0.04 mmol (*S*)-PipPhos, 0.02 mmol tri-*o*-tolylphosphine, 0.1 mmol salt, 4 mL toluene, 60 °C, 50 bar H_2, 24h. [b]Conversion was determined by GC. [c]Enantiomeric excess was determined by GC analysis with Chiralsil DEX CB column.[d]1 mol% $(CH_3)_4NI$ added.

It was observed that all tested chloride salts induced high enantioselectivities. The presence of cesium fluoride completely inhibited the reaction (Entry 5), whereas potassium bromide and tetrafluoroborate (Entries 6, 8) led to high conversions although the enantioselectivities were somewhat lower. The addition of potassium iodide also had a negative effect on the enantioselectivity (Entry 7). Since with potassium chloride irreproducible results were obtained, piperidine hydrochloride was chosen as the additive for further screenings. Under the same conditions tetramethylammonium iodide was tested as additive. Excellent conversions and high *ee* was obtained (74%, Entry 9). This was an interesting finding, since tetraalkylammonium salts are known to stabilize metal nanoparticles.[54]

To obtain more information on the relative effect of the additional ligand and the salt, all possible combinations in toluene and in dichloromethane

were screened in the asymmetric hydrogenation of 2-methylquinoline **1** (Table 2.10).

Table 2.10 Effect of the addition of piperidine hydrochloride on the *ee* in the asymmetric hydrogenation of **1**[a]



1 **1a**

Entry	*Solvent*	*L**	*L*	*Additive*	*Conv.*[b] *(%)*	*ee*[c] *(%)*
1	CH_2Cl_2	PipPhos	-	-	100	18
2	CH_2Cl_2	PipPhos	-	Piperidine·HCl	100	83
3	CH_2Cl_2	PipPhos	P(*o*-tol)$_3$	-	100	69
4	CH_2Cl_2	PipPhos	P(*o*-tol)$_3$	Piperidine·HCl	100	89
5	toluene	PipPhos	-	-	100	36
6	toluene	PipPhos	-	Piperidine·HCl	100	63
7	toluene	PipPhos	P(*o*-tol)$_3$	-	100	67
8	toluene	PipPhos	P(*o*-tol)$_3$	Piperidine·HCl	100	83

[a]Reaction conditions: 1 mmol quinoline **1**, 0.01 mmol $[Ir(COD)Cl_2]_2$, 0.04 mmol (*S*)-PipPhos **L1a**, 0.02 mmol tri-*o*-tolylphosphine, 0.1 mmol piperidine hydrochloride, 4 mL solvent, 60 °C, 50 bar H_2, 24h. [b]Conversion was determined by GC. [c]Enantiomeric excess was determined by GC analysis with Chiralsil DEX CB column.

The use of 10 mol% of piperidine hydrochloride as the sole additive in dichloromethane led to an increase in enantioselectivity from 18 to 83% (Entries 1, 2). In the mixed ligand system, the addition of chloride improved the enantioselectivity from 69 to 89% (Entries 3, 4). A similar effect is observed in toluene where using piperidine hydrochloride as the sole additive led to an increase in the enantioselectivity from 36 to 63% (Entries 5, 6), whereas adding the hydrochloride salt to the mixed ligand system led to an increase in *ee* from 67 to 83% (Entries 7, 8).

The effect of the amount of added piperidine salt on the conversion and enantioselectivity was also studied (Table 2.11). It turned out that as long as the amount of the piperidine·HCl is higher then 2 mol%, results stayed in the same range, with the best enantioselectivity still being 83% (Entry

1). However, we decided to always use 10 mol% because of easier handling and more precise weighing of the salt.

Table 2.11 Effect of the amount of piperidine hydrochloride on the *ee* in the asymmetric hydrogenation of **1**[a]

Entry	*Amount of Piperidine·HCl (%)*	*Conv.[b] (%)*	*ee[c] (%)*
1	2	97	83
2	4	90	79
3	8	97	80
4	20	98	81
5	100	98	81
6	200	96	81

[a]Reaction conditions: 1 mmol quinoline **1**, 0.01 mmol $[Ir(COD)Cl_2]_2$, 0.04 mmol (*S*)-PipPhos **L1a**, 0.02 mmol tri-*o*-tolylphosphine, 4 mL toluene, 60 °C, 50 bar H_2, 24h. [b]Conversion was determined by GC. [c]Enantiomeric excess was determined by GC analysis with Chiralsil DEX CB column.

2.6.2 Iodine as additive

Osborn reported in 1990 that iridium-iodo-hydride species are observed in the hydrogenation of imines (Figure 2.9).[55]

transoid *cisoid*

Figure 2.9 and cisoid iodo-iridium active species observed in the hydrogenation of imines

Over the last decade it has been reported in the literature that iodine increases the enantioselectivity in the iridium catalyzed asymmetric hydrogenation.[15,24-28,30,56] Presumably iodine oxidizes Ir(I) species to more catalytically active Ir(III) species. In some cases it has been shown that no conversion was obtained in the reactions without iodine.[15,30,56] Zhang described recently ruthenium catalyzed hydrogenation of sulfonyl ketones, where addition of iodine improves the enantioselectivity of the reaction.[57]

We were inspired by these findings and therefore decided to test the effect of iodine on the hydrogenation of 2-methylquinoline **1** using Ir/PipPhos catalytic system.

When 10% of iodine was added to the hydrogenation of 2-methylquinoline **1** (1 mmol scale, 1% $[Ir(COD)Cl]_2$, 60 °C, 70 bar H_2) product with 79% conversion and 7% *ee* was obtained after 24h. A similar result was obtained when the mixture of PipPhos **L1a** and tri-*o*-tolylphosphine **L12** was used (78% conversion and 10% *ee*). ^{31}P NMR showed no signal of the phosphoramidite ligand after the reaction (146 ppm). A new signal appeared at 13 ppm. It is likely that iodine oxidizes the phosphoramidite ligand during the reaction and therefore no high *ee* can be obtained.

2.6.3 Amines as additives

Using an achiral catalyst, Crabtree and co-workers developed an iridium catalyst that was able to rapidly hydrogenate olefins.[58,59] Crabtree's catalyst (Figure 2.10), catalyzes the hydrogenation of 1-hexene 100 times faster than Wilkinson's catalyst. It also hydrogenates tri- and even tetrasubstituted olefins; Wilkinson's catalyst is inactive towards the latter.[58] Crabtree's catalyst also stands out in the diastereoselective, functional-group-directed hydrogenation of cyclic alkenes, consistently controlling the stereochemistry of the new stereocenter relative to the directing group better than the related rhodium catalysts.[60]

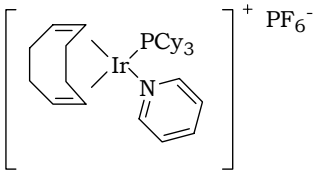


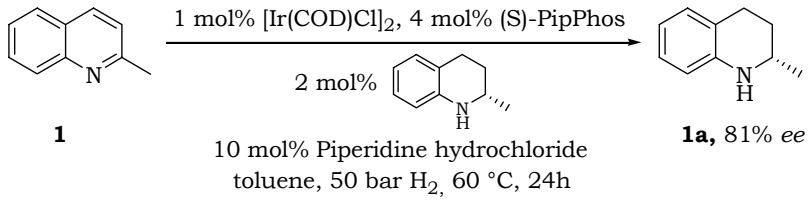
Figure 2.10 Crabtree's catalyst

Therefore, we decided to examine a possibility to use a mixture of a phosphoramidite ligand with an amine in the asymmetric hydrogenation of 2-methyl quinoline **1** (*in situ* formation of Crabtree-like catalyst). Unfortunately, triethylamine in combination with PipPhos **L1a** led to poor

conversion and 28% *ee*, while use of pyridine with PipPhos **L1a** gave 44% of racemic product.

2.6.4 Tetrahydroquinoline as additive

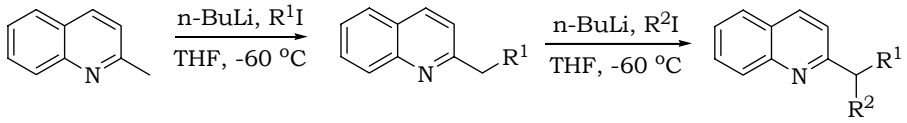
It was also examined whether the product of the hydrogenation also behaves as a ligand coordinating to iridium possibly even stronger than the phosphoramidite and in this way causes autocatalytic reaction (Scheme 2.7). In this experiment 2 mol% of the enantioenriched tetrahydroquinoline (80% *ee*) was added to the reaction mixture. The result of the hydrogenation did not improve, as full conversion overnight and 81% *ee* was obtained (83% *ee* is obtained without addition of tetrahydroquinoline).



Scheme 2.7 Asymmetric hydrogenation of 2-methylquinoline **1** with addition of the enantioenriched product of the hydrogenation

2.7 Synthesis of substrates

In order to test the scope of the hydrogenation, several 2-substituted quinoline substrates were synthesized (Scheme 2.8). Reactions were performed starting from 2-methylquinoline **1**, by deprotonation with butyllithium and subsequent trapping with the alkyl iodide. Products were isolated in 63-88% yield after purification, with the exception of benzyl-quinoline that was isolated in only 23% yield.



1

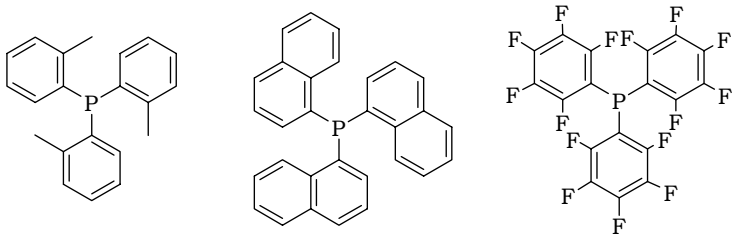
4, R^1 = Me
6, R^1 = i-Pr
7, R^1 = Bu
8, R^1 = Pentyl
9, R^1 = Ph

5, R^1 = Me, R^2= Me

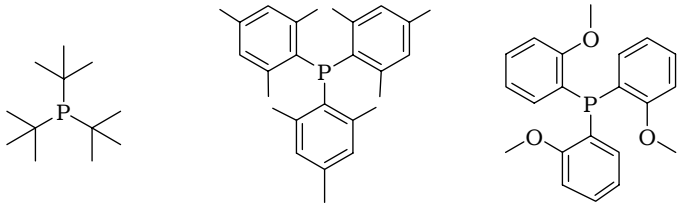
Scheme 2.8 Synthesis of 2-substituted quinolines

2.8 Scope

Under the optimized conditions, a variety of substituted quinolines was hydrogenated using the $[Ir(COD)Cl]_2$/PipPhos/phosphine/piperidine hydrochloride catalytic system in toluene or dichloromethane. Six different achiral phosphines were tested on the selected substrates (Figure 2.11). The phosphines applied were the ones giving the best result in the hydrogenation of 2-methylquinoline **1**. The best results are summarized in Table 2.12



L12 **L15** **L16**

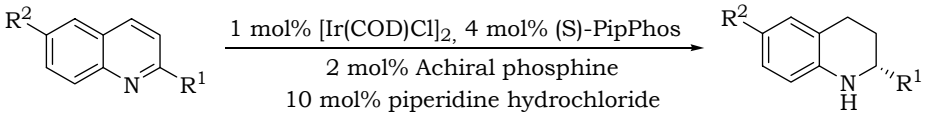


L17 **L22** **L23**

Figure 2.11 Phosphines used in the testing of the scope of the reaction

All quinolines studied were hydrogenated with high conversions and enantioselectivities. The best results were accomplished with 2-methyl and *i*-Pr substituted quinoline (**1**, **5**, 89% *ee*, Entries 1, 3), while the lowest enantioselectivity was obtained with benzyl-quinoline **9** (76% *ee*, Entry 7). Introduction of electron donating or withdrawing substituents in the 6-position did not affect the enantioselectivity significantly (Entries 9-11), whilst introduction of longer alkyl chains resulted in a small drop of *ee* (Entries 5 and 6).

Table 2.12 Asymmetric hydrogenation of 2- and 2,6-substituted quinolines using (*S*)-PipPhos and achiral phosphines[a]



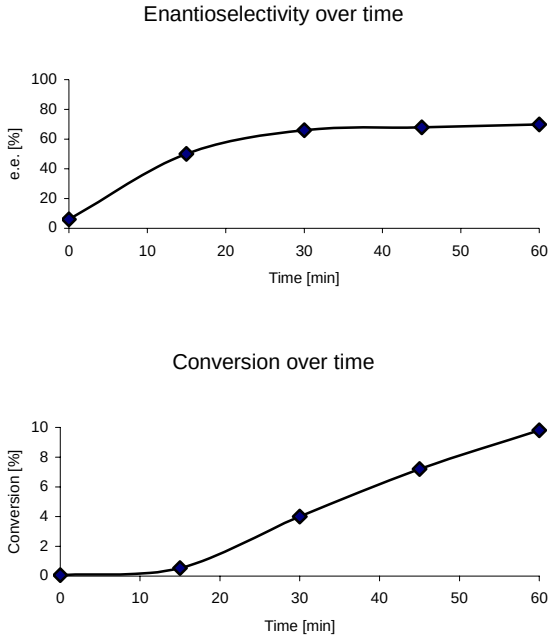
1, 4-13 **1a, 4a-13a**

Entry	*Solvent*	*R^1/R^2*	*Phosphine*	*Conv.*[b] *(%)*	*ee*[c] *(%)*	*Config.*[d]
1	CH_2Cl_2	Me/H (**1a**)	**L12**	100	89	(*S*)
2	CH_2Cl_2	Et/ H (**4a**)	**L12**	100	88	(*S*)
3	toluene	*i*-Pr/H (**5a**)	**L12**	100	89	(*R*)
4	toluene	*i*-Bu/H (**6a**)	**L12**	98	86	nd
5	CH_2Cl_2	*n*-Pentyl/H (**7a**)	**L12**	100	83	(*S*)
6	CH_2Cl_2	*n*-Hexyl/H (**8a**)	**L12**	100	78	nd
7	CH_2Cl_2	Benzyl/H (**9a**)	**L12**	100	76	nd
8	toluene	Ph/H (**10a**)	**L16**	88	88	(*S*)
9	CH_2Cl_2	Me/Me (**11a**)	**L12**	100	85	(*S*)
10	CH_2Cl_2	Me/MeO (**12a**)	**L12**	73	82	(*S*)
11	CH_2Cl_2	Me/F (**13a**)	**L24**	100	88	(*S*)

[a]Reaction conditions: 1 mmol quinoline, 0.01 mmol $[Ir(COD)Cl_2]_2$, 0.04 mmol (*S*)-PipPhos **L1a**, 0.02 mmol achiral phosphine, 0.1 mmol piperidine hydrochloride, 4 mL solvent, 60 °C, 50 bar H_2, 24h. [b]Conversion was determined by ^1H NMR. [c]Enantiomeric excess was determined by GC and HPLC. [d]Absolute configuration of the products are assigned by measuring optical rotation and comparing it with literature data.

2.9 Kinetics

In order to examine the stability of the catalyst during the reaction, the conversion and enantioselectivity were monitored over time (Figure 2.12). An increase of the enantioselectivity over 24h was observed. The low *ee* at the beginning of the reaction may be explained by the slow formation of the catalytically active species during the first hour (10% of conversion). This is also confirmed by the induction time that is observed in the hydrogenation (Figure 2.12).



[a]Reaction conditions: 1 mmol quinoline **1**, 0.01 mmol $[Ir(COD)Cl]_2$, 0.04 mmol (S)-PipPhos **L1a**, 0.02 mmol tri-o-tolylphosphine, 0.1 mmol piperidine hydrochloride, 4 mL toluene, 24 h. [b]Conversion was determined by GC and enantiomeric excess was determined by GC analysis with Chiralsil DEX CB column.

Figure 2.12 Rate and enantioselectivity as a function of time in the asymmetric hydrogenation of 2-methylquinoline **1**[a]

To overcome this drawback the iridium precursor was pre-stirred in the presence of the ligands and piperidine hydrochloride under the reaction conditions during 1h, followed by the addition of the substrate. Unfortunately, this did not improve the enantioselectivity or change the conversion of the reaction.

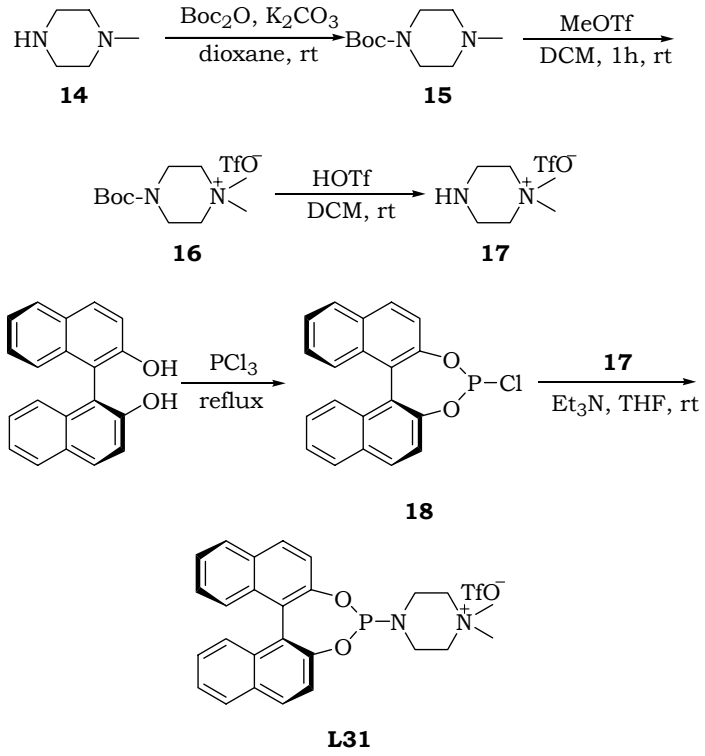
2.10 Mechanistic discussion

In order to gain insight into the mechanism of the reaction, high pressure ^{31}P NMR experiments were performed on the asymmetric hydrogenation of **1** using a mixture of PipPhos **L1a** and achiral phosphine as ligands (2:1) at 60 °C and 25 bar of H_2 pressure. Surprisingly, no mixed ligand iridium species were observed when tri-*o*-tolylphosphine **L12** was used as achiral phosphine. A large tri-*ortho*-tolylphosphine absorption was visible in the ^{31}P-NMR prior to and throughout the hydrogenation reaction. In the case of triphenylphosphine **L11** and PipPhos, mixed ligand species were observed, however, this catalyst gave only 2% conversion in the hydrogenation of **1**. This result suggests that *o*-substituted achiral phosphines are perhaps sterically too demanding for coordination to the iridium together with PipPhos **L1a**, making it impossible to form a mixed ligand complex. In addition, no difference was observed between the ^{31}P NMR spectra of the reactions with and without added piperidine hydrochloride. Despite the significant improvement of the selectivity, the role of the achiral phosphine and chloride salt has not been elucidated until now. However, it is known that iridium catalysts tend to decompose to inactive hydride-bridged clusters in the absence of substrate.[61] If the substrate is a weak ligand, this decomposition can be competitive with hydrogenation. It is conceivable that the chloride salt prevents the formation of poorly active iridium clusters. The role of the added phosphine ligand is even more obscure. It may just serve as a scavenger of traces of oxygen. It is also possible that mixed ligand species are formed in one or more intermediates of the catalytic cycle but not in the resting state, thus making them unobservable.

Mass spectral studies into the nature of the catalyst were hampered by the fact that these catalysts are neutral species and thus lead to feeble signals in ES-MS. To try to solve this problem an analogous catalyst which

carries a positive charge in the ligand was developed. This approach has been used with great success by Chen in his MS study of metathesis catalysts.[62]

Thus, quaternized ligand **L31** was prepared (Scheme 2.9). The synthesis starts with Boc-protection of 1-Methyl-piperazine **14**, followed by methylation with methyl triflate in dichloromethane at rt, and deprotection with triflic acid. Prepared quaternized amine **17** was isolated in 76% yield. (*S*)-BINOL was refluxed in neat PCl_3 in order to obtain chlorophosphite **18**. The solution of prepared chlorophosphite was stirred with **17** in the presence of triethylamine in THF to give the phosphoramidite **L31** in overall 27% yield.

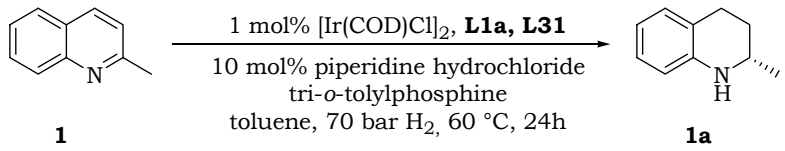


Scheme 2.9 Preparation of quaternized phosphoramidite ligand **34**

Unfortunately, the results in the iridium-catalyzed hydrogenation of 2-methylquinoline **1** with ligand **L31** were dramatically different from the results obtained with PipPhos **L1a** (Table 2.13). Thus, this ligand cannot

be assumed to be a good model compound for PipPhos **L1a**. In spite of this, an ESI-MS analysis of the hydrogenation reactions of 2-methylquinoline was done. In all MS very minor peaks of iridium complexes were observed, none of which could be associated with **L31**. In addition, the spectra showed only very small peaks of the molecular ion of **L31**. No satisfactory explanation for these results was obtained. One possibility is that the majority of the iridium is present in the form of nanoparticles, stabilized by **L31**.

Table 2.13 Asymmetric hydrogenation of 2-methylquinoline **1** using quaternized ligand **L31**[a]



1 **1a**

Entry	***L31*** / ***L1a*** / *P(o-tol)3* / *Cl-* / *Ir*	*Conv.*[b] *(%)*	*ee*[c] *(%)*
1	1 / 1 / 0 / 0 / 1	31	3
2	1 / 1 / 1 / 0 / 1	0	-
3	1 / 1 / 1 / 5 / 1	4	44
4	1 / 1 / 0 / 5 / 1	19	12
5	2 / 0 / 0 / 0 / 1	41	6
6	2 / 0 / 1 / 0 / 1	6	7
7	2 / 0 / 1 / 5 / 1	2	18

[a]Reaction conditions: 1 mmol quinoline **1**, 0.01 mmol $[Ir(COD)Cl]_2$, 4 mL of dichloromethane, 60 °C, 25 bar H_2, 2h. [b]Conversion was determined by GC. [c]Enantiomeric excess was determined by GC analysis with Chiralsil DEX CB column.

Although low enantioselectivities were obtained in the asymmetric hydrogenation of 2-methylquinoline **1** using quaternized ligand **L31**, it was observed that using 2 equivalents of **L31** per iridium atom, hydrogenation is much faster than with PipPhos, giving 41% conversion within 2h (Entry 5). Moreover, using a mixture of **L31** and PipPhos (1:1), the reaction is still significantly faster (Entry 1).

2.11 Conclusion

Various phosphoramidite ligands were tested in the catalytic asymmetric hydrogenation of quinolines. The best result was obtained using monodentate phosphoramidites derived from cyclic amines. When achiral ligands were screened in combination with PipPhos **L1a** in the mixed ligand approach, highest activity was obtained using bulky phosphines and phosphines with substituent in *ortho* position (up to 89%).

The combination $[Ir(COD)Cl]_2$/PipPhos/tri-*o*-tolylphosphine/piperidine hydrochloride is a good catalyst for the asymmetric hydrogenation of 2- and 2,6-substituted quinolines. Full conversions and enantioselectivities up to 89% were obtained at 60 °C and 50 bar of hydrogen pressure within 24h.

We still don't have an answer about the role of a chloride salt. It is plausible that the chloride salt prevents the formation of poorly active iridium clusters. Although we did not observe mixed ligand species, it is possible that they are formed in one or more intermediates of the catalytic cycle but not in the resting state, thus making them unobservable.

2.12 Experimental section

General remarks

All solvents were reagent grade and were dried and distilled, if necessary, following standard procedures. Reagents were purchased from Aldrich, Acros, Merck or Fluka and used as received. Metal precursor $[Ir(COD)Cl]_2$ was purchased from Strem.

High throughput experiment was performed in a Premex 96 autoclave. NMR spectra were obtained on Varian Gemini-200 and Varian AMX400 spectrometers. GC analysis was carried out on an HP6890 using a flame ionization detector, while HPLC analysis was performed on Shimadzu LC-10ADVP HPLC equipped with a Shimadzu SPD-M10AVP diode array detector. The enantiomeric excess was determined by HPLC with chiral columns (Chiralcel AS, AS-H, OJ-H, OD-H,) or by GC with Chiralsil DEX CB, in comparison with racemic products. High resolution mass spectra were recorded on an AEI-MS-902 mass spectrometer. Optical rotations

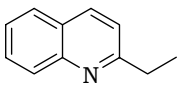
were measured on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100 mL).

The catalysts were prepared in situ. Reaction vessels were filled under air and then flushed with nitrogen before hydrogen pressure was applied. When the metal precursor and the ligand were pre-stirred over 3h under nitrogen, same result was obtained in the hydrogenation reaction. Ligands **L1a**,[38] **L1b**,[38] **L1c**,[38] **L1d**,[38] **L1e**,[63] **L1f**,[63] **L1g**,[63] **L1h**,[64] **L1i**,[63] **L1j**,[38] **L1k**,[38] **L1l**,[65] **L2a**,[63] **L2f**,[63] **L3**,[66] **L5**,[38] **L6**,[63] **L7**,[63] **L8**,[67] **L9**,[68] **L10**[69] were prepared according to the literature procedure. Ligand **L4** is commercially available.

Preparation of 2-quinolines

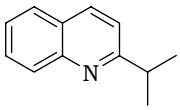
A solution of 2-methylquinoline (3.78 mL, 27.9 mmol) in 50 mL of dry THF was cooled to 60 °C. n-Butyl-lithium (11.2 mL, 2.5 M in hexane, 27.9 mmol) was added dropwise. The reaction mixture was stirred at 60 °C over 1.5h. The alkyl-iodide (27.9 mmol) was added dropwise over 5 min and the reaction mixture stirred overnight at room temperature. The reaction was quenched with water, and the product was extracted with ethyl acetate (2x100 mL). The organic layer was dried over sodium sulphate and filtered. The solvent was removed in vacuo and the product purified by column chromatography on silica.

2-ethyl-quinoline (4)



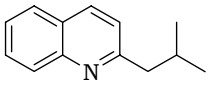
Yellow liquid, 88% yield; ^{1}H NMR (400 MHz, $CDCl_3$) 1.38 (t, J = 7.6 Hz, 3H), 2.99 (q, J = 7.6 Hz, 2H), 7.25 (d, J = 8.4 Hz, 1H), 7.42 – 7.46 (m, 1H), 7.63 – 7.67 (m, 1H), 7.71 – 7.73 (m, 1H), 8.00– 8.05 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 14.9, 33.2, 121.7, 126.5, 127.6, 128.3, 129.7, 130.2, 137.1, 148.8, 164.8 ppm.

2-*i*-propyl-quinoline (5)[70]



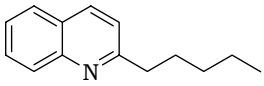
Yellow liquid, 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$) 1.39 (d, J = 7.0 Hz, 6H), 3.27 (heptet, J = 6.9 Hz, 1H), 7.29 – 7.31 (m, 1H), 7.43 – 7.47 (m, 1H), 7.64 – 7.68 (m, 1H), 7.72 – 7.75 (m, 1H), 8.03 – 8.08 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 23.4, 38.2, 120.0, 126.5, 127.8, 128.3, 129.9, 130.1, 137.2, 148.6, 168.5 ppm.

2-*i*-butyl-quinoline (6)[71]



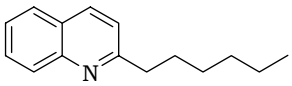
Yellow liquid, 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$) 0.97 (d, J = 6.6 Hz, 6H), 2.21 (nonet, J = 6.7 Hz, 1H), 2.84 (d, J = 7.37 Hz, 2H), 7.22 – 7.24, (m, 1H), 7.43 – 7.47 (m, 1H), 7.64 – 7.68 (m, 1H), 7.74 – 7.76 (m, 1H), 8.01 – 8.07 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 23.5, 30.3, 49.3, 122.9, 126.5, 127.6, 128.4, 129.8, 130.2, 136.8, 148.9, 163.1 ppm.

2-*n*-pentyl-quinoline (7)[70]



Yellow liquid, 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$) 0.90 (t, J = 7.0 Hz, 3H), 1.33 – 1.44 (m, 4H), 1.78 – 1.85 (m, 2H), 2.94 – 2.98 (m, 2H), 7.27 – 7.29 (m, 1H), 7.44 – 7.48 (m, 1H), 7.64 – 7.67 (m, 1H), 7.74 – 7.76 (m, 1H), 8.03 – 8.06 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 15.0, 23.5, 30.7, 32.7, 40.3, 122.3, 126.5, 127.6, 128.4, 129.8, 130.2, 137.1, 148.9, 164.1 ppm.

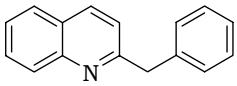
2-*n*-hexyl-quinoline (8)[71]



Yellow liquid, 63% yield; ^{1}H NMR (400 MHz, $CDCl_3$) 0.88 (t, J = 7.0 Hz, 3H), 1.26 – 1.45 (m, 6H), 1.77 – 1.84 (m, 2H), 2.94 – 2.98 (m, 2H), 7.27 – 7.29 (m, 1H), 7.44 – 7.48 (m, 1H), 7.65 – 7.69 (m, 1H), 7.74 – 7.76 (m, 1H), 8.03

– 8.06 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 15.0, 23.5, 30.2, 31.0, 32.7, 40.3, 122.3, 126.5, 127.6, 128.4, 129.8, 130.2, 137.1, 148.9, 164.1 ppm.

2-benzylquinoline (9)[72]

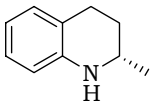


Yellow liquid, 23% yield; ^{1}H NMR (400 MHz, $CDCl_3$) 4.34 (s, 2H), 7.22 – 7.26 (m, 2H), 7.29 – 7.33 (m, 4H), 7.50 (t, *J* = 7.98 Hz, 1H), 7.71 (t, *J* = 8.44 Hz, 1H), 7.76 (d, *J* = 8.08 Hz, 1H), 8.02 (d, *J* = 8.46 Hz, 1H), 8.11 (d, *J* = 8.50 Hz, 1H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$) 46.5, 122.5, 127.0, 127.5, 127.7, 128.5, 129.6, 129.9, 130.2, 130.5, 137.5, 140.1, 148.7, 162.2 ppm.

General Experimental Procedure for Hydrogenation

A mixture of $[Ir(COD)Cl]_2$ (6.72 mg, 0.01 mmol), (*S*)-PipPhos (15.98 mg, 0.04 mmol), achiral phosphine (0.02 mmol), substrate (1 mmol) and piperidine hydrochloride (12.16 mg, 0.1 mmol) were dissolved in 4 mL of solvent in a glass vial. The vial was placed in a stainless steel autoclave. Hydrogenation was performed at 60 °C under 50 bar of hydrogen pressure for 24h. After cooling the autoclave, hydrogen pressure was carefully released. The reaction mixture was flushed over a short silica column. Solvent was removed in vacuo and conversion was determined by GC or NMR. The crude product was purified by chromatography (Silica gel, heptane/EtOAc = 4/1).

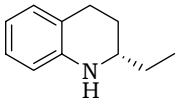
(*S*)-2-Methyl-1,2,3,4-tetrahydroquinoline (1a)[27]



94% yield, 89% *ee*, $[\alpha]_D$ = -84.3 (c 1.19, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) 1.31 (d, *J* = 6.4 Hz, 3H), 1.66 – 1.80 (m, 1H), 1.97 – 2.08 (m, 1H), 2.85 – 2.97 (m, 2H), 3.45 – 3.54 (m, 1H), 3.73 (br, 1H), 6.55 – 6.70 (m, 1H), 6.70 – 6.77 (m, 1H), 7.06 – 7.12 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) 22.5, 26.5, 30.0, 47.0, 113.9, 116.8, 121.0, 127.0, 129.2, 144.7 ppm; HRMS Calcd. for $C_{10}H_{13}N$ (M^+) 147.1048, found 147.1051; GC Chiralsil DEX CB

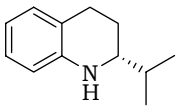
(initial temp. 95 °C for 15 min, then 5 °C/min to 180 °C, 180 °C for 10 min), t_1 = 25.9 min, t_2 = 26.0 min.

(*S*)-2-Ethyl-1,2,3,4-tetrahydroquinoline (4a)[27]



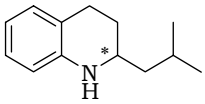
88% *ee*, $[\alpha]_D$ = -76.9 (*c* 1.01, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) 1.00 (t, *J* = 7.6 Hz, 3H), 1.48 – 1.70 (m, 3H), 1.93 – 2.06 (m, 1H), 2.67 – 2.92 (m, 2H), 3.12 – 3.25 (m, 1H), 3.94 (br, 1H), 6.49 – 6.66 (m, 2H), 6.94 – 7.01 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) 10.0, 26.4, 27.5, 29.4, 53.0, 113.9, 116.8, 121.3, 126.7, 129.2, 144.7 ppm; HRMS Calcd. for $C_{11}H_{15}N$ (M^+) 161.1204, found 161.1213; HPLC (OJ-H, eluent:heptane/*i*-PrOH = 95/5, detector: 254 nm, flow rate: 0.5 mL/min), t_1 = 17.6 min, t_2 = 19.1 min.

(*R*)-2-Isopropyl-1,2,3,4-tetrahydroquinoline (5a)[27]



89% *ee*, $[\alpha]_D$ = -54.1 (*c* 0.84, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) 1.03 (d, *J* = 4.9 Hz, 3H), 1.07 (d, *J* = 4.9 Hz, 3H), 1.67 – 1.82 (m, 2H), 1.91 – 2.02 (m, 1H), 2.79 – 2.88 (m, 2H), 3.05 – 3.14 (m, 1H), 3.82 (br, 1H), 6.52 – 6.69 (m, 2H), 6.99 – 7.06 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) 18.2, 18.5, 24.4, 26.6, 32.4, 57.2, 113.9, 116.6, 121.3, 126.6, 129.1, 144.9 ppm; HRMS Calcd. for $C_{12}H_{17}N$ (M^+) 175.1361, found 175.1363; HPLC (OD-H, eluent:heptane/*i*-PrOH = 99/1, detector: 254 nm, flow rate: 0.5 mL/min), t_1 = 14.7 min, t_2 = 17.4 min.

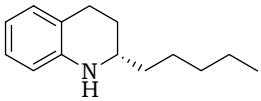
(-)-2-Isobutyl-1,2,3,4-tetrahydroquinoline (6a)[27]



86% *ee*, $[\alpha]_D$ = -73.4 (*c* 1.23, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) 1.01 (d, *J* = 6.4 Hz, 6H), 1.38 – 2.04 (m, 5H), 2.79 – 2.90 (m, 2H), 3.35 – 3.41 (m, 1H), 3.8 (br, 1H), 6.50 – 6.62 (m, 1H), 6.63 – 6.70 (m, 1H), 6.99 – 7.06 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) 22.4, 23.1, 24.4, 26.4, 28.5, 45.8, 49.1,

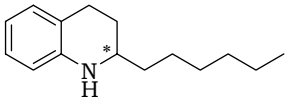
114.0, 116.8, 121.3, 126.6, 129.2, 144.6 ppm; HRMS Calcd. for $C_{13}H_{19}N$ (M^+) 189.1517, found 189.1519; HPLC (OJ-H, eluent:heptane/*i*-PrOH = 95/5, detector: 254 nm, flow rate: 0.5 mL/min), t_1 = 12.8 min, t_2 = 16.9 min.

(*S*)-2-Pentyl-1,2,3,4-tetrahydroquinoline (7a)[27]



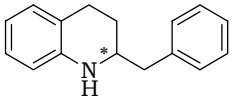
83% *ee*, $[\alpha]_D$ = -68.9 (*c* 1.08, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) 0.97 (t, *J* = 6.8 Hz, 3H), 1.39 – 1.75 (m, 9H), 1.95 – 2.08 (m, 1H), 2.78 – 2.88 (m, 2H), 3.22 – 3.33 (m, 1H), 3.80 (br, 1H), 6.50 – 6.61 (m, 1H), 6.61 – 6.69 (m, 1H), 6.98 – 7.05 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) 14.0, 22.6, 25.3, 26.4, 28.0, 31.9, 36.6, 51.5, 113.9, 116.8, 121.3, 126.6, 129.2, 144.7 ppm; HRMS Calcd. for $C_{14}H_{21}N$ (M^+) 203.1674, found 203.1682; HPLC (AS, eluent:100% heptane, detector: 254 nm, flow rate: 1 mL/min) t_1 = 6.9 min, t_2 = 11.0 min.

(-)-2-Hexyl-1,2,3,4-tetrahydroquinoline (8a)



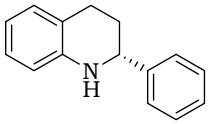
78% *ee*, $[\alpha]_D$ = -56.6 (*c* 0.99, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) 0.96 (t, *J* = 6.6 Hz, 3H), 1.36 – 1.74 (m, 11H), 1.95 – 2.05 (m, 1H), 2.78 – 2.88 (m, 2H), 3.23 – 3.31 (m, 1H), 3.80 (br, 1H), 6.50 – 6.61 (m, 1H), 6.61 – 6.68 (m, 1H), 6.97 – 7.05 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) 14.1, 22.6, 25.6, 26.4, 28.0, 29.4, 31.8, 36.7, 51.5, 113.9, 116.8, 121.3, 126.6, 129.2, 144.7 ppm; HRMS Calcd for $C_{15}H_{23}N$ (M^+) 217.1830, found 217.1830; HPLC (OD, eluent:heptane/*i*-PrOH = 99/1, detector: 254 nm, flow rate: 0.5 mL/min), t_1 = 12.1 min, t_2 = 13.4 min.

(-)-2-Benzyl-1,2,3,4-tetrahydroquinoline (9a)



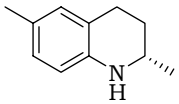
76% *ee*, $[\alpha]_D$ = -99.2 (*c* 1.01, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) 1.75 – 1.90 (m, 1H), 2.04 – 2.17 (m, 1H), 2.73 – 2.99 (m, 4H), 3.52 – 3.65 (m, 1H), 3.81 (br, 1H), 6.46 – 6.66 (m, 1H), 6.66 – 6.74 (m, 1H), 7.00 – 7.07 (m, 2H), 7.31 – 7.48 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) 26.1, 28.1, 42.9, 52.5, 114.1, 117.1, 121.1, 126.4, 126.6, 128.5, 129.2, 138.4, 144.3 ppm; HRMS Calcd for $C_{16}H_{17}N$ (M^+) 223.1361, found 223.1361; HPLC (OJ-H, eluent:heptane/*i*-PrOH = 95/5, detector: 254 nm, flow rate: 0.5 mL/min), t_1 = 23.5 min, t_2 = 25.6 min.

(*S*)-2-Phenyl-1,2,3,4-tetrahydroquinoline (10a)[27]



88% *ee*, $[\alpha]_D$ = +69.9 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) 2.04 – 2.16 (m, 2H), 2.72 – 2.97 (m, 2H), 4.06 (br, 1H), 4.45 (dd, *J* = 3.6 Hz, 1H), 6.54 – 6.65 (m, 1H), 6.65 – 6.72 (m, 1H), 7.02 – 7.09 (m, 2H), 7.31 – 7.45 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) 26.3, 30.9, 56.29, 113.9, 117.1, 120.8, 126.5, 126.9, 127.4, 128.5, 129.3, 144.7, 144.7 ppm; HRMS Calcd. for $C_{15}H_{15}N$ (M^+) 209.1204, found 209.1202; HPLC (AS-H, eluent:heptane/*i*-PrOH = 95/5, detector: 254 nm, flow rate: 0.5 mL/min), t_1 = 9.0 min, t_2 = 13.9 min.

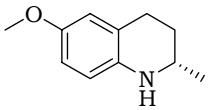
(*S*)-2,6-Dimethyl-1,2,3,4-tetrahydroquinoline (11a)[27]



88% *ee*, $[\alpha]_D$ = -87.2 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) 1.21 (d, *J* = 6.2 Hz, 3H), 1.49 – 1.69 (m, 1H), 1.89 – 1.99 (m, 1H), 2.22 (s, 3H), 2.63 – 2.89 (m, 2H), 3.29 – 3.45 (m, 1H), 3.56 (br, 1H), 6.40 – 6.44 (m, 1H), 6.78 – 6.81 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) 20.3, 22.5, 26.5, 30.3, 47.2, 114.2, 121.1, 126.1, 127.1, 129.7, 142.4 ppm; HRMS Calcd. for $C_{11}H_{15}N$

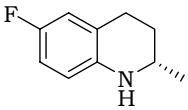
(M^+) 161.1204, found 161.1213; GC Chiralsil DEX CB (initial temp. 95 °C for 15 min, then 5 °C/min to 180 °C, 180 °C for 10 min), t_1 = 27.6 min, t_2 = 27.9 min.

(*S*)-6-Methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (12a)[27]



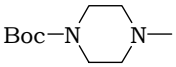
82% *ee*, $[\alpha]_D$ = -80.4 (*c* 1.01, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) 1.20 (d, *J* = 6.0 Hz, 3H), 1.50 – 1.67 (m, 1H), 1.86 – 1.98 (m, 1H), 2.64 – 2.86 (m, 2H), 3.25 – 3.38 (m, 1H), 3.73 (s, 3H), 6.43 – 6.57 (m, 1H) 6.57 – 6.63 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) 22.5, 26.8, 30.2, 47.4, 55.7, 112.7, 114.5, 115.2, 122.4, 138.8, 151.7 ppm; HRMS Calcd. for $C_{11}H_{15}NO$ (M^+) 177.1154, found 177.1161; GC Chiralsil DEX CB (initial temp. 95 °C for 15 min, then 5 °C/min to 180 °C, 180 °C for 10 min), t_1 = 31.5 min, t_2 = 31.7 min.

(*S*)-6-Fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (13a)[27]



88% *ee*, $[\alpha]_D$ = -37.3 (*c* 0.53, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) 1.21 (d, *J* = 6.4 Hz, 3H), 1.46 – 1.66 (m, 1H), 1.86 – 1.98 (m, 1H), 2.63 – 2.92 (m, 2H), 3.27 – 3.43 (m, 1H), 3.54 (br, 1H), 6.36 – 6.43 (m, 1H), 6.63 – 6.72 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) 22.4, 26.6, 29.8, 47.2, 112.9, 113.2, 114.6, 114.7, 115.1, 115.4 ppm; HRMS Calcd. for $C_{10}H_{12}FN$ (M^+) 165.0954, found 165.0950; GC Chiralsil DEX CB (initial temp. 95 °C for 15 min, then 5 °C/min to 180 °C, 180 °C for 10 min), t_1 = 26.9 min, t_2 = 27.1 min.

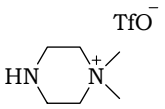
2,2-Dimethyl-propionic acid 4-methyl-piperazin-1-yl ester (15)



To a solution of 1-methyl-piperazine (5 g, 50 mmol) in dioxane (100 mL) di-*tert*-butyl dicarbonate (11.98 g, 55 mmol) and potassium carbonate (7.59 g, 55 mmol) were added and reaction mixture was stirred overnight at rt. The resulting mixture was washed with water (100 mL) and the water layer

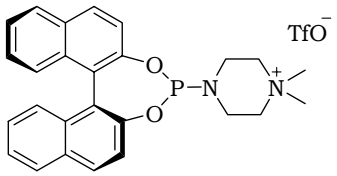
was extracted with ethyl acetate (100 mL). The combined organic layers were dried on anhydrous magnesium sulfate and filtered. The solvent was removed in vacuo, and **15** was isolated as yellow oil in 92% yield (9.1 g).
^{1}H NMR (400 MHz, $CDCl_3$) 1.32 (s, 9H), 2.15 (s, 3H), 2.20 (t, *J* = 3.8 Hz, 4H), 3.29 (t, *J* = 1.3 Hz, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 28.5, 46.3, 54.9, 79.6, 154.8 ppm; HRMS Calcd. for $C_6H_{15}N_2$ (M^+) 200.1525, found 200.1518.

Trifluoro-methanesulfonate 1,1-dimethyl-piperazin-1-ium (17)



To a solution of 4-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (7.1g, 35.4 mmol) in dry dichloromethane (50 mL), methyl triflate was added dropwise (4 mL, 35.4 mmol). The reaction mixture was stirred at rt over 1h, followed by addition of triflic acid (4.97 mL, 56.2 mmol). After 1h, the solvent was decanted and 50 mL of methanol was added. After stirring for 15 min the precipitated white solid was filtered off and dried. Quaternized amine **17** was isolated in 82% yield (7.63 g).
^{1}H NMR (400 MHz, D_2O) 3.20 (s, 6H), 3.59 (br, 4H), 3.64 (br, 4H), 4.63 (br, 1H) ppm; ^{13}C NMR (100 MHz, D_2O) 38.0, 52.2, 58.2, 123.0 ppm; ^{19}F (376 MHz, D_2O) -79.3 ppm; HRMS Calcd. for $C_6H_{15}N_2$ (M^+-OTf^-) 115.12298, found 115.12302.

(*S*)-Trifluoro-methanesulfonate 4-(3,5-dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)-1,1-dimethyl-piperazin-1-ium (L31)



In a Schlenk tube (*S*)-BINOL (1.5 g, 5.24 mmol) was refluxed in neat phosphorus trichloride (5 mL) overnight. After cooling the reaction mixture, the excess of phosphorus trichloride was distilled off and the resulting phosphorus chloride **18** was washed with dry toluene (3 x 5 mL), and dissolved in dry THF (5 mL). In another Schlenk tube quaternized

amine **17** (1.38 g, 5.24 mmol) and triethylamine (726 μL, 5.24 mmol) were dissolved in 5 mL of THF. The solution of **18** was then added to the solution of **17** and triethylamine at 0 °C. After 10 min, the reaction mixture was warmed to rt and stirred overnight. The precipitated crystals were filtered off and ether was added (10 mL). Newly formed white precipitate was filtered off and washed with dichloromethane. Pure phosphoramidite **L31** was isolated in 36% yield (1.09 g).
$[\alpha]_D$ = -75.3 (c 1.0, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) 3.18 – 3.28 (m, 14H), 7.25 – 7.49 (m, 8H), 7.86 – 7.96 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 38.1, 38.3, 51.8, 62.4 (d, *J* = 3.8 Hz), 121.0, 121.4, 122.7, 123.6, 125.2, 126.4, 126.6, 126.7, 126.8, 128.4, 128.6, 130.7, 130.9, 131.0, 131.5, 132.3, 132.6, 148.4 ppm; ^{31}P NMR (162 MHz) 142.9 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) -78.9 ppm. HRMS Calcd. for $C_{26}H_{26}O_2N_2P$ (M^+-OTf) 429.17264, found 429.17215.

2.13 References

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